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WO 01/16166 A2(54) Title: **POLYPEPTIDES, COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE**

(57) Abstract: The present invention provides, among other things, a polypeptide, and a pharmaceutically acceptable salt thereof, that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, a nucleic acid that encodes such a polypeptide and can be expressed in a cell, a nucleic acid that comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for such a polypeptide, an antibody that is specific to such a polypeptide, and anti-antibody thereto, a composition comprising such a polypeptide, nucleic acid, antibody or an anti-body and a carrier therefor, a composition comprising a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to a specified polypeptide sequence, a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, a mammal in need thereof, and a method of removing IL-6 ligand from a body fluid of an animal.

POLYPEPTIDES COMPRISING IL-6 LIGAND-BINDING
RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS,
ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to polypeptides comprising IL-6 ligand-binding receptor domains, nucleic acids encoding such polypeptides, antibodies, compositions comprising such polypeptides, nucleic acids, 10 or antibodies, and methods of use.

BACKGROUND OF THE INVENTION

Interleukin-6 (IL-6) is a cytokine that is produced in response to various stimulators and is responsible for 15 a variety of biological activities, including the stimulation of B- and T-cell growth and differentiation (Muraguchi et al., *J. Exp. Med.* 167: 332 (1988)), production of acute-phase proteins in response to inflammation or tissue injury (Gauldie et al., *PNAS USA* 20 84: 7251 (1987); Geiger et al., *Eur. J. Immunol.* 18: 717 (1988)), multilineage hematopoiesis, osteoclast formation, maturation of megakaryocytes, and platelet 25 production. These biological activities are initiated when IL-6 binds to the extracellular portion of the interleukin-6 receptor, which is variously referred to as the interleukin-6 α subunit (IL-6R α) or B-cell stimulating factor receptor (BSF-2 receptor). When IL-6 binds to IL-6R α , a complex is formed. The complex then binds to the extracellular portion of the interleukin-6 30 receptor known as gp130, which is also referred to as the

interleukin-6 β subunit (IL-6R β). The resulting complex then transmits the IL-6 signal intracellularly.

The precursor of the IL-6 receptor reportedly comprises 468 amino acids (Yamasaki et al., *Science* 241: 5 825-828 (1988)). The mature IL-6 receptor reportedly comprises 449 amino acids (Yamasaki et al. (1988), *supra*).

Abnormal expression of IL-6 has been implicated in the pathogenesis of a variety of diseases, including 10 multiple myeloma, plasmacytoma, hematological diseases such as plasma cell dyscrasias, leukemia and lymphoma (including non-Hodgkin's lymphoma and Lennert's T-cell lymphoma (Kishimoto, *Blood* 74: 1 (1989)), mesangial proliferative glomerulonephritis, polyclonal B-cell 15 activation conditions, allergic diseases (Type I-IV), rheumatoid arthritis (Hirano et al., *Eur. J. Immunol.* 18: 1797 (1988)), diabetes, multiple sclerosis, SLE, septic shock, bacterial infection, viral infection, post-menopausal osteoporosis, chronic immune deficiency and 20 autoimmune diseases (*Med. Immunol.* 15: 195-201 (1988)), including organ-specific and systemic diseases and AIDS, inflammatory diseases, and Cattleman's disease. In addition, IL-6 production has been associated with cardiac myxoma and cervical cancer (Kishimoto et al., 25 *Ann. Rev. Immunol.* 6: 485 (1988)) *in vivo* and myelomas, histiocytomas and promyelocytic leukemia (Taga et al., *J. Exp. Med.* 166: 967 (1987)) *in vitro*. Attempts to abrogate the effects of abnormal expression of IL-6 can be made at its site of production or at its target. 30 In view of the above, there remains a need for materials and methods for identifying and designing

agents that inhibit IL-signaling and for treating diseases involving IL-6 signaling prophylactically and therapeutically. It is an object of the present invention to provide such materials and methods. This 5 and other objects and advantages, as well as additional inventive features, will become apparent from the detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

10 The present invention provides, among other things, a polypeptide, and a pharmaceutically acceptable salt thereof, that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. In one embodiment, the polypeptide has the formula $R^1R^2R^3L^1L^2L^3R^4R^5$, and pharmaceutically acceptable salts thereof, in which R^1 is hydrogen, $R^3C(O)-$ or R^3 , and does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α -chain of the IL-6 receptor and is not linked to the moiety $-R^2R^3L^1L^2L^3R^4$ via a glycanyl 15 residue or via a proprionyl residue, R^2 is hydrogen, a polypeptide of from 1 to about 100 amino acid residues, NHR^6 or R^6 , and R^3 is a pharmaceutically acceptable 20 substituent group.

In another embodiment, the polypeptide has the 25 formula $R^{10}R^{11}XVL^{12}L^{13}VR^{14}$, in which R^{10} and R^{14} , independently, are pharmaceutically acceptable substituents, R^{11} is a naturally-occurring or synthetic amino acid residue that has an acidic or neutral side-chain under physiological conditions, X is any naturally- 30 occurring or synthetic amino acid residue, and L^{13} is leucinyl or isoleucinyl.

In yet another embodiment, the polypeptide has the formula $R^{20}R^{21}L^*R^*Y^*R^*A^*E^*R^*S^*R^{22}$, in which R^{20} and R^{22} are pharmaceutically acceptable substituents, R^{21} is a naturally-occurring or synthetic amino acid residue that 5 has a basic or neutral side-chain under physiological conditions, L^* , Y^* , E^* and S^* are independently any naturally-occurring or synthetic amino acid residue, R^* is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological 10 conditions, and A^* is alaninyl, glycinyll, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β -alaninyl or α -aminoisobutyryl.

In still yet another embodiment, the polypeptide comprises at least $I^*A^*I^*V^*L^*R^*F^*$ but less than about 200 15 amino acid residues that have a sequence that is identical to an amino acid sequence of the α -chain of the IL-6 receptor, in which I^* , L^* , and V^* are independently a naturally-occurring or synthetic amino acid residue having a side-chain consisting of a C_1 - C_6 straight chain 20 or C_1 - C_6 branched alkyl moiety, R^* is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological conditions, A^* is alaninyl, glycinyll, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β -alaninyl or 25 α -aminoisobutyryl, and F^* is tyrosinyl, phenylalaninyl, tryptophanyl or α -aminoisobutyryl, with the proviso that at least four of the seven substituents of $I^*A^*I^*V^*L^*R^*F^*$ are selected such that I^* is isoleucinyl, A^* is alaninyl, V^* is valinyl, L^* is leucinyl, R^* is arginanyl, and F^* is 30 phenylalaninyl.

In a further embodiment, the polypeptide comprises up to 200 amino acid residues that are identical to an amino acid residue sequence of the β -chain of the IL-6 receptor and comprises the sequence SVIILKYNIQY,

5 TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL,
QLPVDVQNGFIRNYTIFYRTIIGN, or
IVVPVCLAFLLTLLGVLFCKFNKRDLIKHIWPNVPDPSKSHIA, any one of
which can comprise from one to about six conservative or
neutral replacements. The polypeptide can further
10 comprise a pharmaceutically acceptable substituent.

Also provided by the present invention is a nucleic acid that encodes an above-described polypeptide, wherein the polypeptide preferably consists of naturally-occurring amino acid residues. The nucleic acid encoding

15 the polypeptide can be expressed in a cell. The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes secretion of at least the polypeptide by a cell in which the nucleic acid is
expressed. Alternatively, the nucleic acid comprises or
20 encodes an antisense nucleic acid molecule or a ribozyme that is specific for a nucleotide sequence in a nucleic acid encoding the specified amino acid sequence in an above-described polypeptide.

Further provided by the present invention is a
25 composition comprising an above-described polypeptide or nucleic acid and a carrier therefor. Another composition provided by the present invention is a composition comprising an antibody to an above-described polypeptide, an anti-antibody to an above-described polypeptide, or a
30 solid support matrix to which is attached an above-described polypeptide or an anti-antibody to the

polypeptide sequence RRLLLRL, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY,

5 TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and

IVVPVCLAFLLTLLGVLFCFNKRDLIKHHIWPVNVPDPSKSHIA.

Also provided by the present invention is a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal. The method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of an above-described polypeptide, a nucleic acid encoding such a polypeptide or an antibody to such a polypeptide.

15 In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of an animal. The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to which is attached an above-described polypeptide or an

20 anti-antibody to the polypeptide sequence RRLLLRL, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL,

25 QLPVDVQNGFIRNYTIFYRTIIGN, and

IVVPVCLAFLLTLLGVLFCFNKRDLIKHHIWPVNVPDPSKSHIA.

Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the solution can be contacted with a solid support matrix to

30 which is attached a means to remove the polypeptide or

anti-antibody to which is bound IL-6 ligand from the bodily fluid.

BRIEF DESCRIPTION OF THE DRAWING

5 Figure 1 depicts a listing of synthetic amino acids available (from Bachem, King of Prussia, PA) for incorporation into polypeptides and compounds of the present invention.

10 DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, among other things, a polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present invention is predicated in part on a detailed 15 study of a series of synthetic polypeptides having the same or similar amino acid sequence as that of IL-6 receptor, in which the ability of each synthetic polypeptide to bind to the IL-6 ligand was measured first in a high-throughput *in vitro* assay, and then confirmed 20 (for at least a subpopulation of the synthetic polypeptides of greater interest) by measuring the ability of the synthetic peptide to inhibit the growth, replication, and survival of IL-6-dependent cells grown in a cellular growth medium comprising IL-6 ligand. 25 Those of skill in the art will recognize that the ability of any particular polypeptide to inhibit IL-6 signaling or function *in vivo* can be easily and rapidly determined using either the techniques employed in the examples provided below, or by using another suitable testing 30 technique, such as the B9 cell growth and signal transduction assays known in the art (see, e.g., Halimi

et al., *Eur.Cytokine Netw.* 6: 135-43 (1995)). The skilled artisan would expect the results of such *in vitro* assays to be reasonably predictive of *in vivo* utility.

While not intending to be bound by any particular theory, it is believed that the present inventive polypeptide, and compositions comprising the same, inhibit the ability of IL-6 ligand to bind to the soluble IL-6 receptor or the membrane-bound IL-6 receptor, by binding to unbound IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling, IL-6-dependent cellular responses (including changes in one or more of the group consisting of cellular metabolism, cellular growth, cellular replication, and cellular survival; the term "cellular metabolism" includes the ability of the cell to affect neighboring cells by secretion of biomolecules (e.g., paracrines, or exocrines), and/or display of cell-surface biomolecules (e.g., proteins or lipids)).

In each embodiment provided herein, a letter indicates the standard amino acid designated by that letter, and a letter followed directly by an asterisk (*) preferably represents the amino acid represented by the letter (e.g., N represents asparaginyl and T represents threoninyl), or a synthetic or naturally-occurring conservative or neutral substitution therefor, unless otherwise specified. Additionally, in accordance with convention, all amino acid sequences provided herein are given from left to right, such that the first amino acid is amino-terminal and the last is carboxyl-terminal. The synthesis of polypeptides, whether synthetic (i.e., chemical) or biological, is within the skill in the art.

It is within the skill of the ordinary artisan to select synthetic and naturally-occurring amino acids that effect conservative or neutral substitutions for any particular naturally-occurring amino acids. The skilled artisan desirably will consider the context in which any particular amino acid substitution is made, in addition to considering the hydrophobicity or polarity of the side-chain, the general size of the side chain and the pK value of side-chains with acidic or basic character under physiological conditions. For example, lysine, arginine, and histidine are often suitably substituted for each other, and more often arginine and histidine. As is known in the art, this is because all three amino acids have basic side chains, whereas the pK value for the side-chains of lysine and arginine are much closer to each other (about 10 and 12) than to histidine (about 6). Similarly, glycine, alanine, valine, leucine, and isoleucine are often suitably substituted for each other, with the proviso that glycine is frequently not suitably substituted for the other members of the group. This is because each of these amino acids are relatively hydrophobic when incorporated into a polypeptide, but glycine's lack of an α -carbon allows the phi and psi angles of rotation (around the α -carbon) so much conformational freedom that glycinyl residues can trigger changes in conformation or secondary structure that do not often occur when the other amino acids are substituted for each other. Other groups of amino acids frequently suitably substituted for each other include, but are not limited to, the group consisting of glutamic and aspartic acids; the group consisting of

phenylalanine, tyrosine and tryptophan; and the group consisting of serine, threonine and, optionally, tyrosine. Additionally, the skilled artisan can readily group synthetic amino acids with naturally-occurring 5 amino acids.

In the context of the present invention, a polypeptide is "substantially identical" to another polypeptide if it comprises at least about 80% identical amino acids. Desirably, at least about 50% of the 10 non-identical amino acids are conservative or neutral substitutions. Also, desirably, the polypeptides do not differ in length (i.e., due to deletion mutations) by more than about 10%.

In a first embodiment, the present invention 15 provides a polypeptide of the formula $R^1R^*R^*L^*L^*L^*R^*R^2$ (domain I), and pharmaceutically acceptable salts thereof. In this embodiment, R^1 is selected from the group consisting of hydrogen, $R^3C(O)-$, and R^3 . However, R^1 does not comprise an amino acid residue sequence that 20 is identical to an amino acid residue sequence of the α -chain of the IL-6 receptor and is not linked to the moiety $-R^1R^*L^*L^*L^*R^*$ via a glycanyl residue or a propionyl residue. Preferably, R^1 is not linked to the moiety $-R^1R^*L^*L^*L^*R^*$ via either a glycanyl, propionyl, butyryl, 25 or alaninyl residue, and, more preferably, R^1 does not comprise an amino acid residue sequence that is greater than 50% identical to the amino acid residue sequence RWAGM- at the site of linkage to the moiety $-R^1R^*L^*L^*L^*R^*$.

R^* is independently selected from the group 30 consisting of arginanyl, naturally-occurring arginanyl equivalents, and synthetic arginanyl equivalents.

L' is independently selected from the group consisting of leucinyl, naturally-occurring leucinyl equivalents, and synthetic leucinyl equivalents.

R^2 is selected from the group consisting of hydrogen,
5 a polypeptide of from 1 to about 100 amino acid residues,
 $-NHR^3$, and R^3 .

The substituent R³ is a pharmaceutically acceptable group. R³ is independently selected with respect to size or length and secondary structure so that the present inventive polypeptide is able to bind to the IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling under physiological conditions.

An amino acid residue equivalent thereof comprises a primary amine linked by one to three, preferably two, and more preferably one, methylenyl group(s) linked to a carboxylic acid, i.e., $\text{NH}_2\text{-}(\text{CHR}^a)_{1-3}\text{-COO}^-$, preferably $\text{NH}_2\text{-}(\text{CHR}^a)_2\text{-COO}^-$ and more preferably $\text{NH}_2\text{-}(\text{CHR}^a)\text{-COO}^-$. An amino residue (or its equivalent) is linked via a peptide bond ($-\text{C}(\text{O})\text{NH}-$) to another amino acid residue (or its equivalent) or a polypeptide. An amino acid residue equivalent is an amino acid residue in which R^a is selected to have the same charge under physiological conditions as the amino acid residue, and, preferably, is selected to have a similar number of atoms as the side-chain substituent of the amino acid residue, i.e., plus or minus 50%, preferably plus or minus 20%. All amino acid residue equivalents preferably have only one R^a moiety that is not hydrogen (except for glycyl equivalents for which R^a can be, and preferably is, repetitively selected as hydrogen, e.g., 3-amino propionic acid; $\text{NH}_2\text{-}(\text{CH}_2)_2\text{-COO}^-$). By way of example, an

argininyl equivalent residue is preferably selected from the group consisting of argininyl and lysinyl because (1) these residues are naturally-occurring and are encoded by a mammalian gene or genome, and (2) these residues have

5 (a) similar sizes (arginine having 7 side-chain atoms (excluding hydrogen atoms) and lysine having 5, $((5-7)/(7) \times 100\% = 28\%)$), and (b) these residues are bases having similar pK values (about 12 and 10, respectively).

An argininyl residue or an argininyl equivalent residue can be either natural or synthetic. In addition to an argininyl residue *per se*, a natural amino acid residue equivalent to an argininyl residue includes, but is not limited to, histidinyl and lysinyl, and is preferably lysinyl. A synthetic amino acid residue

10 equivalent to an argininyl residue includes, but is not limited to, d-forms of argininyl, lysinyl, and histidinyl residues, as well as L- and D-, but preferably L-, ornithinyl, citrullinyl, and homoargininyl residues. The skilled artisan will recognize additional argininyl

15 equivalents from Figure 1.

A leucinyl residue or a leucinyl equivalent residue can be either natural or synthetic. Leucinyl equivalents include, but are not limited to, leucinyl, isoleucinyl, alaninyl, valinyl, norleucinyl, norvalinyl, sarcosinyl,

20 β -alaninyl, and α -aminoisobutyryl. The skilled artisan will recognize additional leucinyl equivalents from Figure 1. Of course, in any given polypeptide, substitutions are preferably limited in number. For example, in the polypeptide R'R'L'L'L'R', all of the R' residues and all of the L' residues are most preferably argininyl and leucinyl, respectively; less preferably,

one residue is other than argininyl or leucinyl, yet less preferably two or three residues are not argininyl or leucinyl, and least preferably four to six residues are not argininyl or leucinyl. Accordingly, a most preferred 5 residue for R' is an argininyl residue.

Similarly, L' can be independently selected from the group consisting of leucinyl, isoleucinyl, and valinyl; preferably L' is leucinyl or isoleucinyl; and most preferably, L' is leucinyl. Additionally, L' can 10 optionally be a d-form amino acid residue, and/or a synthetic residue such as, e.g., an α -aminoisobutyryl residue.

The substituent R³ can be any suitable pharmaceutically acceptable substituent. A pharmaceutically acceptable substituent need not, but can 15 provide a function, such as homing to sites of inflammation, increasing the solubility in water of the present inventive polypeptide, and protecting side-chains of amino acid residues from oxidative or chemical attack. 20 For example, a pharmaceutically acceptable substituent can be a biopolymer, such as a polypeptide, an RNA, a DNA, or a polysaccharide. Suitable polypeptides comprise fusion proteins, an antibody or fragment thereof, a cell adhesion molecule or a fragment thereof, or a peptide 25 hormone. Suitable polysaccharides comprise polyglucose moieties, such as starch and derivatives thereof, such as heparin. R³ also can be any suitable lipid or lipid-containing moiety, such as a lipid of a liposome or a vesicle, saccharide or disaccharide, or even a lipophilic 30 moiety, such as a prostaglandin, a steroid hormone, or a derivative of either of the foregoing. Additionally, R³

can be a nucleotide or a nucleoside, such as nicotine adenine dinucleotide or thymine. R^3 also can be a vitamin, such as vitamin C, thiamine, or nicotinic acid.

5 A pharmaceutically acceptable substituent can be a synthetic organic moiety, such as t-butyl carbonyl, an acetyl moiety, quinine, or polystyrene and another biologically acceptable polymer. A pharmaceutically acceptable substituent also can be R^4 , wherein R^4 is selected from the group consisting of a

10 C_1 - C_{18} alkyl, a C_2 - C_{18} alkenyl, a C_2 - C_{18} alkynyl, a C_6 - C_{18} aryl, a C_7 - C_{18} alkaryl, a C_7 - C_{18} aralkyl, and a C_3 - C_{18} cycloalkyl, wherein any of the foregoing R^3 groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from

15 the group consisting of nitrogen, oxygen, and sulfur.

R^4 can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate

20 moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1 - C_8 monoalkylamine moiety, a C_1 - C_8 dialkylamine moiety, and a C_1 - C_8 trialkylamine moiety.

25 A preferred polypeptide of the first embodiment $R^1R^2R^3L^1L^2L^3R^4R^5$ is RRLLLRL, wherein R is arginanyl and L is leucanyl. In a more preferred embodiment, R^2 of the formula $R^1R^2R^3L^1L^2L^3R^4R^5$ is a -(serinyl-valinyl- R^5), and R^5 is selected from the group consisting of hydrogen, a

30 polypeptide of from 1 to about 98 amino acid residues,

-NHR⁴, and R⁴, wherein R⁴ is as defined above and can be substituted as described above.

In a second embodiment, the present invention provides a polypeptide of the formula R¹⁰R¹¹XVL¹²L¹³VR¹², as well as pharmaceutically acceptable salts thereof. This embodiment is predicated, at least in part, on two surprising and unexpected discoveries. First, that a second domain of the α -chain of the IL-6 receptor that has the ability to bind to the IL-6 ligand comprises an important amino acid residue sequence -VLLV-, which naturally occurs in the context TKAVLLVRF. Second, that the binding affinity of this second domain is substantially increased if the lysinyl residue (in the larger subsequence) is replaced by an amino acid residue that does not have a side-chain that is basic under physiological conditions.

In this second embodiment, R¹⁰ and R¹² are pharmaceutically acceptable substituents. Examples of pharmaceutically acceptable substituents are provided above with respect to R³.

R¹¹ is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or neutral side-chain under physiological conditions. For example, R¹¹ can be selected from either the group consisting of alaninyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glycyl, isoleucinyl, leucinyl, methioninyl, phenylalaninyl, prolinyl, serinyl, threoninyl, tryptophanyl, tyrosinyl, and valinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, β -alaninyl, α -aminoisobutyryl, γ aminopentane-1,5-dioyl,

homoserinyl, hydroxyprolinyl, α -carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl.

Similarly, X can be any synthetic or naturally-occurring amino acid residue, such as any synthetic or naturally-occurring amino acid residue that has an acidic or neutral side-chain under physiological conditions. That is, X can be selected from the group consisting of suitable R¹¹ residues, as well as from among the group consisting of arginanyl, lysanyl, and histidinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, β -alaninyl, α -aminoisobutyryl, γ -aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, γ -carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, O-phosphotyrosinyl, ornithinyl, citrullinyl, and homoargininyl. However, X is preferably independently selected from the group denoted by R¹¹.

In the context of the formula R¹⁰R¹¹XVL^{*2}L^{*2}VR¹², V is valinyl and L^{*2} is leucinyl or isoleucinyl, and preferably leucinyl. As noted above, each substituent of the polypeptide is selected such that this present inventive polypeptide inhibits the binding of IL-6 with IL-6 receptor under physiological conditions.

The pharmaceutically acceptable group R¹² can optionally be the substituent R¹³-R¹⁴. Where R¹² is R¹³-R¹⁴, R¹³ is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions, including, but not limited to norleucinyl, sarcosinyl, β -alaninyl, α -aminoisobutyryl, γ -aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, α -

carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. Where R^{12} is $R^{13}-R^{14}$, R^{14} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, 5 -NHR¹⁵, and R¹⁵. R¹⁵ is a pharmaceutically acceptable substituent group (see R³, *supra*). Preferably, R¹³ is selected from the group consisting of naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions. Alternatively, 10 R¹³ is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C₁-C₆ straight-chained or branched alkyl moiety; for example, from the group consisting of glycanyl, alananyl, isoleucanyl, leucanyl, 15 valanyl, norleucanyl, sarcosanyl, β -alananyl, and α -aminoisobutyryl. The polypeptide in which R¹³ is alananyl is among the preferred polypeptides of the second embodiment.

In one polypeptide of the second embodiment, R¹⁵ is 20 R¹⁶, and R¹⁶ is selected from the group consisting of hydrogen, a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₇-C₁₈ cycloalkyl, wherein any of the foregoing R¹⁶ groups 25 that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

30 Optionally, R¹⁶ can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate

moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a 5 C₁-C₈ trialkylamine moiety.

In another polypeptide of the second embodiment, R¹⁰ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, R¹⁷C(O)-, and R¹⁷, wherein R¹⁷ is a pharmaceutically 10 acceptable substituent group (see R³, *supra*).

Similarly to R¹⁶, R¹⁷ can be selected from the group consisting of hydrogen, a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the 15 foregoing R¹⁷ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur. In a preferred embodiment, R¹⁷ is hydrogen.

20 Optionally, R¹⁷ can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a 25 pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

In a third embodiment, the present invention 30 provides a polypeptide of the formula R²⁰R²¹L'R'Y'R'A'E'R'S'R²². This embodiment is predicated, at

least in part, on three surprising and unexpected discoveries. First, that a third domain within the IL-6 receptor has the ability to bind to the IL-6 ligand and this domain has the essential core amino acid residue 5 sequence -LRAERS-, which naturally occurs in the larger subsequence -FELRAERSKT. Second, that the affinity of this domain for the IL-6 ligand can be substantially enhanced if the acidic side chain of the first glutamyl residue in the larger sequence is eliminated or 10 preferably is replaced by a small hydrophobic side-chain (e.g., as possessed by alanine). Third, that the lysinyl residue is preferably present and more preferably has a side-chain that is basic under physiological conditions.

In this third embodiment, R^{20} and R^{22} are 15 pharmaceutically acceptable substituents. The substituent R^{21} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions, which includes, but clearly is 20 not limited to, norleucinyl, norvalinyl, sarcosinyl, β -alaninyl, α -aminoisobutyryl, homoserinyl, hydroxyprolinyl, ornithinyl, citrullinyl, and homoargininyl. Preferably, R^{21} is alaninyl.

Additionally, L^* , Y^* , E^* , and S^* are each 25 independently selected from the group consisting of synthetic and naturally-occurring amino acid residues. L^* is preferably leucinyl or isoleucinyl. More preferably, L^* is leucinyl. The substituent Y^* is preferably selected from the group consisting of tyrosinyl, phenylalaninyl, 30 tryptophanyl, and α -aminoisobutyryl. More preferably, Y^* is tyrosinyl or phenylalaninyl, and most preferably,

tyrosinyl. The substituent E* is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having acidic side-chains under physiological conditions. For example, E* can be selected 5 from the group consisting of glutamyl, aspartyl, γ aminopentane-1,5-dioyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. More preferably, E* is selected from the group consisting of glutamyl, aspartyl, and γ aminopentane-1,5-dioyl. Yet 10 more preferably, E* is glutamyl. The substituent S* is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl, and preferably is serinyl. The substituent A* is selected from the group consisting of alaninyl, glycyl, and 15 valinyl, and preferably is alaninyl.

Preferably, R²⁰ is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, R²³C(O)-, and R²³. Similarly, R²² is preferably selected from the group consisting of a 20 polypeptide of from 1 to about 100 amino acid residues, hydrogen, -NHR²³, and R²³.

The substituent R²³ can be selected from the group consisting of a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, 25 and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R²³ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

30 R²³ can be substituted by one to about six substituents, which can be the same or different,

selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate 5 moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

R' is independently selected from the group consisting of synthetic or naturally-occurring amino acid 10 residues having a side-chain that is basic under physiological conditions; for example, arginanyl, lysanyl, ornithanyl, citrullanyl, or homoarginanyl. Preferably, R' is selected from the group consisting of arginanyl and lysanyl. More preferably, R' is arginanyl.

15 A* is selected from the group consisting of alananyl, glycanyl, isoleucanyl, leucanyl, valanyl, norleucanyl, norvalanyl, sarcosanyl, β -alananyl, and α -aminoisobutyryl. Preferably, A* is alananyl.

20 Additionally, the polypeptide of the third embodiment of the present invention can comprise additional polypeptides or protein motifs. Preferably, the present inventive polypeptide does not comprise more than about 200, and preferably more than about 50, additional amino acid residues that have an amino acid 25 residue sequence that is identical (or at least 60% identical over a span of five or ten amino acid residues) to another amino acid residue sequence from the same chain of the IL-6 receptor.

30 In a fourth embodiment, the present invention provides a polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under

physiological conditions. The sequence comprises at least a polypeptide of the formula $I^*A^*I^*V^*L^*R^*F^*$. This embodiment is predicated, at least in part, on the surprising and unexpected discovery that a fourth domain 5 of the IL-6 receptor occurs in the membrane-associated region of the receptor, and this domain is centered about a region of the receptor having an amino acid residue sequence of IAIVLRFK. This embodiment is further predicated on the surprising and unexpected discovery 10 that this domain is highly tolerant of amino acid residue substitutions. For example, the basic residues of this sequence (i.e., arginanyl and lysinyl) can be replaced by a non-conservative alaninyl substitution, which has the surprising effect of increasing the affinity of the 15 domain for the IL-6 ligand.

In this fourth embodiment I^* , L^* , and V^* are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1 - C_6 straight-chain 20 or branched alkyl moiety.

R^* is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions. For example, R^* can be selected 25 from the group consisting of arginanyl, lysinyl, ornithinyl, citrullinyl, and homoargininyl. When R^* is to be translated from a nucleic acid, R^* preferably is selected from the group consisting of arginanyl and lysinyl. R^* is more preferably arginanyl.

30 A^* is selected from the group consisting of alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl,

norvalinyl, sarcosinyl, β -alaninyl, and α -aminoisobutyryl.

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and 5 α -aminoisobutyryl.

Preferably, at least four of the seven substituents, more preferably at least five substituents, yet more preferably at least six substituents of I'A'I'V'L'R'F*, are selected such that I* is isoleucinyl, A* is alaninyl, V* 10 is valinyl, L* is leucinyl, R* is arginyl, and F* phenylalaninyl. Of course, all seven amino acid residues can be selected such that I'A'I'V'L'R'F* is IAIVLRFK. The polypeptide is preferably selected such that it is small enough to bind effectively to IL-6 and does not comprise 15 unnecessary extra atoms (making synthesis and processing of the polypeptide easier). The polypeptide preferably comprises less than about 200 amino acid residues, alternatively less than about 100 amino acid residues, alternatively less than about 30 amino acid residues, and 20 alternatively less than about 16 amino acid residues that have a sequence that is identical to that of a region of the α -chain of the IL-6 receptor.

Surprisingly, the affinity of the polypeptide for binding with IL-6 increases if any one, preferably two, 25 and more preferably three, amino acid residues are bound via peptide bonds to the carboxyl-terminus of the sequence I'A'I'V'L'R'F*. Accordingly, the polypeptide preferably comprises at least the sequence IAIVLRFKXX in which X is any synthetic or naturally-occurring amino 30 acid residue, as defined above, and preferably a synthetic or naturally-occurring amino acid residue of

the formula $\text{NH}_2\text{-}(\text{CHR}^a)\text{-COO}^-$. Optionally, the sequence can comprise an amino-terminal tripeptide of the formula LLC- , or conservatively or neutrally substituted equivalents of LLC- . In this regard, the sequence can 5 comprise at least the sequence LLCIAIVLRFK .

Additionally, the sequence can comprise at least the sequence FGTLLCIAIVLRFKKT .

A fifth embodiment of the present invention is predicated on the surprising and unexpected discovery 10 that the amino acid sequence SVIILKYNIQY , which is a subsequence of the β -chain amino acid sequence of the IL-6 receptor, is critical in the binding between IL-6 ligand and IL-6 receptor. Accordingly, the present invention also provides a polypeptide that inhibits the 15 binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present inventive polypeptide of this fifth embodiment comprises the sequence SVIILKYNIQY and has an amino acid residue sequence of up to about 200 amino acid residues, 20 preferably about 100 residues, more preferably about 50 residues, and optionally no or essentially no additional residues, that are identical to the β -chain of the IL-6 receptor or alternatively are at least about 60% identical over a span of about five or ten contiguous 25 amino acid residues.

Biochemical analysis of this sequence revealed that the binding interaction is somewhat stronger if the sequence SVIILKYNIQY is extended on the amino terminus to include the sequence PSIK- . Accordingly, the present 30 invention also provides a polypeptide of this fifth embodiment comprising the sequence PSIKSVIILKYNIQY .

Similar analyses further defined a region governing the binding between IL-6 ligand and its receptor. These analyses resulted in the identification and provision of polypeptides comprising the sequences WTNPSIKSVIILKYNIQY 5 and KLTWTNPSIKSVIILKYNIQY, and up to about 200 amino acid residues that have an identical residue sequence to the sequence of the β -chain of the IL-6 receptor. Preferably, the polypeptides comprising the recited sequences comprise up to about 100 amino acid residues, 10 more preferably, up to about 50 amino acid residues, from the IL-6 receptor β -chain sequence. Optionally, the polypeptide comprises no other, or essentially no other, sequence of amino acid residues that has an identical sequence to the sequence of the IL-6 receptor β -chain 15 over a continuous stretch of five, or more preferably three, amino acid residues other than the sequences explicitly recited above. Additionally, the present inventive sequences preferably do not comprise a region of higher than about 60% homology to the IL-6 receptor 20 over a stretch of at least five or ten contiguous amino acid residues, outside the region of the IL-6 receptor β -chain sequences explicitly recited above.

Alternatively, the present inventive β -chain polypeptides comprise a sequence consisting essentially 25 of the recited sequence and polypeptides from other sources or origins that primarily contribute a function that is not directly related to IL-6 function or signaling.

In additional (sixth, seventh, and eighth) 30 embodiments, the present invention provides a polypeptide of up to about 200 amino acid residues having a sequence

that is identical to a portion of the sequence
TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL,

QLPVDVQNGFIRNYTIFYRTIIGN, or

IVVPVCLAFLLTLLGVLFCKFNKRDLIKKHIWPVNVPDPSKSHIA, and that

5 inhibits the binding of IL-6 ligand with IL-6 receptor
under physiological conditions. The portion of the
sequence can be any suitable size. For example, the
portion of the amino acid sequence can be about a 6-mer,
about a 12-mer, about an 18-mer, or about a 24-mer. An
10 "n"-mer, as is understood in the art, is an oligopolymer
consisting of "n" monomeric components or residues.

Thus, a polypeptide comprising a portion of any of the
preceding sequences that is a 6-mer, would comprise an
amino acid sequence of any six adjacent residues of any
15 one of the three preceding amino acid sequences.

Preferably, the polypeptide comprises no more than about
100 amino acid residues, and more preferably no more than
about 50 amino acid residues, having a sequence identical
to that of the IL-6 receptor β -chain.

20 Conservative or neutral amino acid substitutions
that do not destroy the ability of any of the above-
described polypeptides to bind to IL-6 can be made. The
replacement residues that substitute for the amino acid
residues explicitly recited above can be either synthetic
25 or naturally-occurring. Preferably, the number of
substitutions is kept to a minimum, e.g., from 1 to about
6 conservative or neutral substitutions, and more
preferably from 1 to about 3 conservative or neutral
amino acid residue substitutions. While the residues
30 substituted for the recited amino acid residues can be
natural or synthetic, natural residues are preferred in

those instances in which it is desirable for the amino acid residues to be encoded by a nucleic acid.

Additionally, any embodiment of the foregoing present inventive polypeptide can further comprise a 5 pharmaceutically acceptable substituent, which is selected so that the polypeptide retains the ability to inhibit the binding of IL-6 ligand with IL-6 receptor under physiological conditions.

Also provided by the present invention is a nucleic 10 acid that encodes an above-described polypeptide, which consists of naturally-occurring amino acid residues. The nucleic acid can be expressed in a cell.

In another embodiment, the present invention also provides a vector comprising a nucleic acid molecule as 15 described above. A nucleic acid molecule as described above can be cloned into any suitable vector and can be used to transduce, transform, or transfect any suitable host. The selection of vectors and methods to construct them are commonly known to persons of ordinary skill in 20 the art and are described in general technical references (see, in general, "Recombinant DNA Part D," *Methods in Enzymology*, Vol. 153, Wu and Grossman, eds., Academic Press (1987)). Desirably, the vector comprises regulatory sequences, such as transcription and 25 translation initiation and termination codons, which are specific to the type of host (e.g., bacterium, fungus, plant, or animal) into which the vector is to be inserted, as appropriate and taking into consideration whether the vector is DNA or RNA. Preferably, the vector 30 comprises regulatory sequences that are specific to the genus of the host. Most preferably, the vector comprises

regulatory sequences that are specific to the species of the host and is optionally optimized for the expression of an above-described polypeptide.

Constructs of vectors, which are circular or linear, 5 can be prepared to contain an entire nucleic acid sequence as described above or a portion thereof ligated to a replication system that is functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived from ColE1, 2 μ plasmid, λ , SV40, bovine 10 papilloma virus, and the like.

Suitable vectors include those designed for propagation and expansion, or for expression, or both. A preferred cloning vector is selected from the group consisting of the pUC series, the pBluescript series 15 (Stratagene, LaJolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clonetech, Palo Alto, CA). Examples of animal expression vectors include pEUK-C1, pMAM and pMAMneo (Clonetech, Palo Alto, CA).

20 An expression vector can comprise a native or nonnative promoter operably linked to a nucleic acid molecule encoding an above-described polypeptide. The selection of promoters, e.g., strong, weak, inducible, tissue-specific and developmental-specific, is within the skill in the art. Similarly, the combining of a nucleic acid molecule as described above with a promoter is also 25 within the skill in the art.

The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes 30 secretion of at least the polypeptide by a cell in which the nucleic acid is expressed. Signal sequences

(alternatively called secretion sequences) are well-known in the art.

Alternatively, the nucleic acid comprises or encodes an antisense nucleic acid molecule or a ribozyme that is 5 specific for a naturally-occurring, specified amino acid sequence of an above-described polypeptide. A nucleic acid sequence introduced in antisense suppression generally is substantially identical to at least a portion of the endogenous gene or gene to be repressed, 10 but need not be identical. Thus, the vectors can be designed such that the inhibitory effect applies to other proteins within a family of genes exhibiting homology or substantial homology to the target gene. The introduced sequence also need not be full-length relative to either 15 the primary transcription product or fully processed mRNA. Generally, higher homology can be used to compensate for the use of a shorter sequence. Furthermore, the introduced sequence need not have the same intron or exon pattern, and homology of non-coding 20 segments will be equally effective.

Ribozymes also have been reported to have use as a means to inhibit expression of endogenous genes. It is possible to design ribozymes that specifically pair with virtually any target RNA and cleave the phosphodiester 25 backbone at a specific location, thereby functionally inactivating the target RNA. In carrying out this cleavage, the ribozyme is not itself altered and is, thus, capable of recycling and cleaving other molecules, making it a true enzyme. The inclusion of ribozyme 30 sequences within antisense RNAs confers RNA-cleaving activity upon them, thereby increasing the activity of

the constructs. The design and use of target RNA-specific ribozymes is described in Haseloff et al., *Nature* 334: 585-591 (1988).

Further provided by the present invention is a
5 composition comprising an above-described polypeptide or nucleic acid and a carrier therefor. Another composition provided by the present invention is a composition comprising an antibody to an above-described polypeptide, an anti-antibody to an above described polypeptide, or a
10 solid support matrix to which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY,
15 TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTLLGVLFCFNKRDLIKHKHIWPVNVPDPSKSHIA.

Antibodies can be generated in accordance with methods known in the art. See, for example, Benjamin, *In Immunology: a short course*, Wiley-Liss, NY, 1996, pp. 436-437; Kuby, *In Immunology*, 3rd. ed., Freeman, NY, 1997, pp. 455-456; Greenspan et al., *FASEB J.* 7: 437-443 (1993); and Poskitt, *Vaccine* 9: 792-796 (1991). Anti-antibodies (i.e., anti-idiotypic antibodies) also can be
20 generated in accordance with methods known in the art (see, for example, Benjamin, *In Immunology: a short course*, Wiley-Liss, NY, 1996, pp. 436-437; Kuby, *In Immunology*, 3rd. ed., Freeman, NY, 1997, pp. 455-456; Greenspan et al., FASEB J., 7, 437-443, 1993; Poskitt,
25 Vaccine, 9, 792-796, 1991; and Madiyalakan et al., *Hybridonor* 14: 199-203 (1995) ("Anti-idiotype induction

therapy""). Such antibodies can be obtained and employed either in solution-phase or coupled to a desired solid-phase matrix. Having in hand such antibodies, one skilled in the art will further appreciate that such 5 antibodies, using well-established procedures (e.g., such as described by Harlow and Lane (1988, supra), are useful in the detection, quantification, or purification of IL-6 ligand, IL-6 receptor, conjugates of each and host cells transformed to produce IL-6 receptor or a derivative 10 thereof. Such antibodies are also useful in a method of prevention or treatment of a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

In view of the above, the present invention also 15 provides a method of producing an antibody to the specific amino acid sequence of an above-described polypeptide. The method comprises administering an above-described polypeptide to an animal. The animal generates anti-polypeptide antibodies. Such an antibody 20 can be administered to an animal to prevent or treat a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

Although nonhuman antibodies are useful for 25 prophylactic or therapeutic treatment in humans, their favorable properties, in certain instances, can be further enhanced and/or their adverse properties further diminished, through "humanization" strategies, such as those recently reviewed by Vaughan, Nature Biotech., 16, 30 535-539, 1998.

Prior to administration to an animal, such as a mammal, in particular a human, an above-described polypeptide, nucleic acid or antibody can be formulated into various compositions by combination with appropriate 5 carriers, in particular, pharmaceutically acceptable carriers or diluents, and can be formulated to be appropriate for either human or veterinary applications.

Thus, a composition for use in the method of the present invention can comprise one or more of the 10 aforementioned polypeptides, nucleic acids or antibodies, preferably in combination with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those skilled in the art, as are suitable methods of administration. The choice of 15 carrier will be determined, in part, by whether a polypeptide or a nucleic acid is to be administered, as well as by the particular method used to administer the composition. One skilled in the art will also appreciate that various routes of administering a composition are 20 available, and, although more than one route can be used for administration, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, there are a wide variety of suitable 25 formulations of compositions that can be used in the present inventive methods.

A composition in accordance with the present invention, alone or in further combination with one or more other active agents, can be made into a formulation suitable for parenteral administration, preferably 30 intraperitoneal administration. Such a formulation can include aqueous and nonaqueous, isotonic sterile

injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions
5 that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

The formulations can be presented in unit dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized)
10 condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneously injectable solutions and suspensions can be prepared from sterile powders, granules, and tablets, as described herein.

15 A formulation suitable for oral administration can consist of liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or fruit juice; capsules, sachets or tablets, each containing a predetermined amount of the active
20 ingredient, as solid or granules; solutions or suspensions in an aqueous liquid; and oil-in-water emulsions or water-in-oil emulsions. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia,
25 gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers.

30 Similarly, a formulation suitable for oral administration can include lozenge forms, which can

comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia; and mouthwashes 5 comprising the active ingredient in a suitable liquid carrier; as well as creams, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

An aerosol formulation suitable for administration 10 via inhalation also can be made. The aerosol formulation can be placed into a pressurized acceptable propellant, such as dichlorodifluoromethane, propane, nitrogen, and the like.

A formulation suitable for topical application can 15 be in the form of creams, ointments, or lotions.

A formulation for rectal administration can be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate. A formulation suitable for vaginal administration can be 20 presented as a pessary, tampon, cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Important general considerations for design of 25 delivery systems and compositions, and for routes of administration, for polypeptide drugs also apply (Eppstein, CRC Crit. Rev. Therapeutic Drug Carrier Systems 5, 99-139, 1988; Siddiqui et al., CRC Crit. Rev. Therapeutic Drug Carrier Systems 3, 195-208, 1987); Banga 30 et al., Int. J. Pharmaceutics 48, 15-50, 1988; Sanders, Eur. J. Drug Metab. Pharmacokinetics 15, 95-102, 1990;

Verhoef, Eur. J. Drug Metab. Pharmacokinetics 15, 83-93, 1990). The appropriate delivery system for a given polypeptide will depend upon its particular nature, the particular clinical application, and the site of drug 5 action. As with any protein drug, oral delivery will likely present special problems, due primarily to instability in the gastrointestinal tract and poor absorption and bioavailability of intact, bioactive drug therefrom. Therefore, especially in the case of oral 10 delivery, but also possibly in conjunction with other routes of delivery, it will be necessary to use an absorption-enhancing agent in combination with a given polypeptide. A wide variety of absorption-enhancing agents have been investigated and/or applied in 15 combination with protein drugs for oral delivery and for delivery by other routes (Verhoef (1990), *supra*; van Hoogdalem, *Pharmac. Ther.* 44: 407-443, (1989); Davis, *J. Pharm. Pharmacol.* 44(Suppl. 1): 186-190, (1992)). Most commonly, typical enhancers fall into the general 20 categories of (a) chelators, such as EDTA, salicylates, and N-acyl derivatives of collagen, (b) surfactants, such as lauryl sulfate and polyoxyethylene-9-lauryl ether, (c) bile salts, such as glycholate and taurocholate, and derivatives, such as taurodihydrofusidate, (d) fatty 25 acids, such as oleic acid and capric acid, and their derivatives, such as acylcarnitines, monoglycerides, and diglycerides, (e) non-surfactants, such as unsaturated cyclic ureas, (f) saponins, (g) cyclodextrins, and (h) phospholipids.

30 Other approaches to enhancing oral delivery of protein drugs can include the aforementioned chemical

modifications to enhance stability to gastrointestinal enzymes and/or increased lipophilicity. Alternatively, the protein drug can be administered in combination with other drugs or substances that directly inhibit proteases 5 and/or other potential sources of enzymatic degradation of proteins. Yet another alternative approach to prevent or delay gastrointestinal absorption of protein drugs is to incorporate them into a delivery system that is designed to protect the protein from contact with the 10 proteolytic enzymes in the intestinal lumen and to release the intact protein only upon reaching an area favorable for its absorption. A more specific example of this strategy is the use of biodegradable microcapsules or microspheres, both to protect vulnerable drugs from 15 degradation, as well as to effect a prolonged release of active drug (Deasy, in Microencapsulation and Related Processes, Swarbrick, ed., Marcell Dekker, Inc.: New York, 1984, pp. 1-60, 88-89, 208-211). Microcapsules also can provide a useful way to effect a prolonged 20 delivery of a protein drug, such as an above-described polypeptide, after injection (Maulding, J. Controlled Release 6, 167-176, 1987).

In view of the above, the present invention further provides a method of prophylactically or therapeutically 25 inhibiting IL-6 signaling in a mammal in need thereof. The method comprises administering to the mammal an IL-6 signaling-inhibiting effective amount of an above-described polypeptide, nucleic acid, or antibody to an above-described polypeptide or a nucleic acid encoding 30 such a polypeptide.

The dose administered to an animal, such as a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic or prophylactic (which desirably, but not necessarily, means absolute prevention as any degree of inhibition of IL-6 signaling in a mammal in need thereof is deemed beneficial) response in the individual over a reasonable time frame. The dose will be determined by the particular polypeptide, nucleic acid or antibody, administered, the severity of any existing disease state, as well as the body weight and age of the individual. The size of the dose also will be determined by the existence of any adverse side effects that may accompany the use of the particular polypeptide, nucleic acid or antibody employed. It is always desirable, whenever possible, to keep adverse side effects to a minimum.

The dosage can be in unit dosage form, such as a tablet or capsule. The term "unit dosage form" as used herein refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a vector, alone or in combination with other active agents, calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the unit dosage forms of the present invention depend on the particular embodiment employed and the effect to be achieved, as well as the pharmacodynamics associated with each polypeptide, nucleic acid or antibody in the host. The dose administered should be an "IL-6 signaling-inhibiting effective amount" of an above-described active

agent to achieve an "effective level" in the individual patient.

With respect to the above methods, sufficient amounts can be determined in accordance with methods known in the art. Similarly, the sufficiency of an immune response in an animal also can be assessed in accordance with methods known in the art. Either one of the above methods can further comprise concurrent, pre- or post-treatment with an adjuvant to enhance the immune response (see, for example, Harlow et al. (1988), *supra*).

Since the "effective level" is used as the preferred endpoint for dosing, the actual dose and schedule can vary, depending on interindividual differences in pharmacokinetics, drug distribution, and metabolism. The "effective level" can be defined, for example, as the blood or tissue level desired in the patient that corresponds to a concentration of one or more polypeptides, nucleic acids or antibodies according to the invention. The "effective level" for a polypeptide, nucleic acid or antibody of the present invention also can vary when the compositions of the present invention are used in combination with other known active agents.

One skilled in the art can easily determine the appropriate dose, schedule, and method of administration for the exact formulation of the composition being used, in order to achieve the desired "effective level" in the individual patient. One skilled in the art also can readily determine and use an appropriate indicator of the "effective level" of a polypeptide, nucleic acid or antibody of the present invention by a direct or indirect

analysis of appropriate patient samples (e.g., blood and/or tissues).

It also will be appreciated by one skilled in the art that an above-described nucleic acid can be inserted 5 *ex vivo* into animal cells, such as mammalian cells, in particular human cells, previously removed from such an animal. Such transformed autologous or homologous host cells, reintroduced into the animal or human, will express directly the corresponding polypeptide *in vivo*. 10 The feasibility of such a therapeutic strategy to deliver a therapeutic amount of an agent in close proximity to the desired target cells has been demonstrated in studies with cells engineered *ex vivo* to express sCD4 (Morgan et al., (1994), *supra*). As an alternative to *ex vivo* 15 insertion of the DNA sequences of the present invention, such sequences can be inserted into cells directly *in vivo*, such as by use of an appropriate viral or other suitable vector. Such cells transfected *in vivo* are expected to produce effective amounts of an above- 20 described polypeptide directly *in vivo*.

Given the present disclosure, it will be additionally appreciated that an above-described nucleic acid sequence can be inserted into suitable nonmammalian host cells, and that such host cells will express 25 therapeutic or prophylactic amounts of the desired polypeptide directly *in vivo* within a desired body compartment of an animal, in particular a human.

In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of a mammal. 30 The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to

which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY,

5 TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTLLGVLFCFNKRDLIKHHIWPVNVPDPSKSHIA.

Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the

10 solution can be contacted with a solid support matrix to which is attached a means to remove the polypeptide or anti-antibody to which is bound IL-6 ligand from the bodily fluid. The method further comprises separating the bodily fluid and the solid support matrix by any

15 suitable means.

Methods of attaching an above-described polypeptide or an anti-antibody to a solid support matrix are known in the art. "Attached" is used herein to refer to attachment to (or coupling to) and immobilization in or on a solid support matrix. See, for example, Harris, in Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York (1992), pp. 1-14) and international patent application WO 91/02714 (Saxinger). Diverse applications and uses of functional polypeptides attached to or immobilized on a solid support matrix are exemplified more specifically for poly(ethylene glycol) conjugated proteins or peptides in a review by Holmberg et al. (In Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York, 1992, pp. 303-324).

EXAMPLES

The following examples further illustrates the present invention but, of course, should not be construed as limiting the scope of the claimed invention in any 5 way.

Synthetic peptide arrays were constructed in 96-well microtiter plates in accordance with the method set forth in WO 91/02714 (Saxinger), and used to test the binding 10 of recombinant human IL-6 that had been labeled with radioactive iodine (radiolabeling by standard methods). After incubating the radiolabeled IL-6 ligand in a well with each synthetic peptide, a washing step was performed to remove unbound label, and the relative level of 15 radioactivity remaining in each well of the plate was evaluated to determine the relative affinity of each peptide for IL-6 ligand. The synthesis of the peptides and the quantity of binding between the synthetic peptides and IL-6 ligand were found to be suitably 20 reproducible, precise, and sensitive. Initial screening of the entire primary sequence of the IL-6 receptor molecule, taken 21 amino acid residues at a time, identified active binding sequences in four regions of the receptor corresponding to amino acid residues 66-86 25 (AAGSHPSRWAGMGRLLLRSV), 136-156 (PRSTPSLTTKAVLLVRKFQNS), 246-266 (SSFYRLRFELRYRAERSKTFT), and 371-391 (GGSLAFGTLLCIAIVLRFKKT) (hereinafter domains I, II, III, and IV).

The authenticity of the binding signal was 30 confirmed, at least for domains I-III, by demonstrating that antibodies that specifically bind to IL-6 ligand

were able to inhibit the binding reactions. The binding between domain IV and IL-6 ligand was not similarly shown to be authentic because domain IV resides in the transmembrane region of the protein and is not believed 5 to have been present in the soluble receptor used as an immunogen to raise the antibodies to IL-6 ligand.

Each of the four binding domains was analyzed in detail, which is set forth in these examples. First, serial truncations (or nested truncations) were performed 10 from each end of the peptides to determine the location of the critical binding residues within each domain. Second, each amino acid residue in the critical regions of each domain were serially replaced by an alaninyl residue to indicate whether the side-chain of the residue 15 at each particular location is likely to be essential or important to the mechanism of binding.

Example 1

This example provides data identifying domain I, as 20 well as amino acid residues that are essential and/or important in the binding of domain I to human IL-6.

<u>Peptide Identifier</u>	<u>Peptide Sequence</u>	<u>Counts/minute bound</u>
A1:	AAGSHPSRWAGMGRLLLLRSV	10739
A2:	AAGSHPSRWAGMGRLLLLRS	9764
A3:	AAGSHPSRWAGMGRLLLLR	8007
A4:	AAGSHPSRWAGMGRLLL	5276
A5:	AAGSHPSRWAGMGRLL	2747
A6:	AAGSHPSRWAGMGRRL	1753
A7:	AAGSHPSRWAGMGR	1344
A8:	AAGSHPSRWAGMGR	1478
A9:	AAGSHPSRWAGMG	1474
A10:	AAGSHPSRWAGM	1444
A11:	AAGSHPSRWAG	1427
A12:	AAGSHPSRWA	1328

A13:	AAGSHPSRW	1520
A14:	AAGSHPSR	1353
A15:	AAGSHPS	1316
A16:	AAGSHP	1574
A17:	AAGSHPSRWAGMGRLLLLRSV	10884
A18:	AGSHPSRWAGMGRLLLLRSV	13393
A19:	GSHPSRWAGMGRLLLLRSV	10994
A20:	SHPSRWAGMGRLLLLRSV	12048
A21:	HPSRWAGMGRLLLLRSV	11969
A22:	PSRWAGMGRLLLLRSV	11087
A23:	SRWAGMGRLLLLRSV	8272
A24:	RWAGMGRLLLLRSV	12069
A25:	WAGMGRLLLLRSV	12166
A26:	AGMGRLLLLRSV	7623
A27:	GMGRLLLLRSV	6820
A28:	MGGRLLLLRSV	7136
A29:	GRLLLLRSV	5367
A30:	RRLLLLRSV	5972
A31:	RLLLLRSV	5464
A32:	LLLRSV	1599
A33:	AAGSHPSRWAGMGRLLLLRSV	10213
A34:	AAGSHPSRWAGMGRLLLLRSA	11797
A35:	AAGSHPSRWAGMGRLLLLRAV	11201
A36:	AAGSHPSRWAGMGRLLLLASV	4895
A37:	AAGSHPSRWAGMGRLLLARSV	7728
A38:	AAGSHPSRWAGMGRLLAARSV	7079
A39:	AAGSHPSRWAGMGRALLRSV	5283
A40:	AAGSHPSRWAGMGRALLRSV	4247
A41:	AAGSHPSRWAGMGRALLRSV	4461
A42:	AAGSHPSRWAGMGRALLRSV	12259
A43:	AAGSHPSRWAGGRLLLLRSV	13521
A44:	AAGSHPSRWAAMGRLLLLRSV	11854
A45:	AAGSHPSRAAGMGRLLLLRSV	8040
A46:	AAGSHPSAWAGMGRLLLLRSV	9523
A47:	AAGSHPARWAGMGRLLLLRSV	11291

These data indicate that the sequence RLLLLR is a critical binding region within domain I, that domain I is preferably flanked on the amino-terminus by a 5 pharmaceutically acceptable substituent equivalent in size to three amino acid residues, e.g., any three amino acid residues, and is preferably flanked on the carboxyl-

terminus by a pharmaceutically acceptable substituent equivalent in size to at least one amino acid residue, and preferably two or three or more amino acid residues.

5 Example 2

This example provides data identifying the critical binding regions of domain II, as well as which residues within the critical binding domain that are essential and/or important in the binding of human IL-6 to IL-6 receptor within domain II.

<u>Peptide Identifier</u>	<u>Peptide Sequence</u>	<u>Counts/minute bound</u>
B1:	PRSTPSLTTKAVLLVRKFQNS	10790
B2:	PRSTPSLTTKAVLLVRKFQN	7930
B3:	PRSTPSLTTKAVLLVRKFQ	7075
B4:	PRSTPSLTTKAVLLVRKF	4689
B5:	PRSTPSLTTKAVLLVRK	3962
B6:	PRSTPSLTTKAVLLVR	4355
B7:	PRSTPSLTTKAVLLV	3401
B8:	PRSTPSLTTKAVLL	1846
B9:	PRSTPSLTTKAVL	1402
B10:	PRSTPSLTTKAV	1216
B11:	PRSTPSLTTKA	1240
B12:	PRSTPSLTTK	1313
B13:	PRSTPSLTT	1053
B14:	PRSTPSLT	930
B15:	PRSTPSL	985
B16:	PRSTPS	1015
B17:	PRSTPSLTTKAVLLVRKFQNS	12347
B18:	RSTPSLTTKAVLLVRKFQNS	12958
B19:	STPSLTTKAVLLVRKFQNS	12150
B20:	TPSLTTKAVLLVRKFQNS	12885
B21:	PSLTTKAVLLVRKFQNS	13294
B22:	SLTTKAVLLVRKFQNS	12645
B23:	LTTKAVLLVRKFQNS	12153
B24:	TTKAVLLVRKFQNS	7014
B25:	TKAVLLVRKFQNS	5753
B26:	TKAVLLVRKFQNS	5226
B27:	KAVLLVRKFQNS	5604
B28:	AVLLVRKFQNS	9073

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B29:	VLLVRKFQNS	9099
B30:	LLVRKFQNS	7205
B31:	LVRKFQNS	2525
B32:	VRKFQNS	1182
B33:	PRSTPSLTTKAVLLVRKFQNS	11699
B34:	PRSTPSLTTKAVLLVRKFQNA	11450
B35:	PRSTPSLTTKAVLLVRKFQAS	13185
B36:	PRSTPSLTTKAVLLVRKFANS	10090
B37:	PRSTPSLTTKAVLLVRKAQNS	11556
B38:	PRSTPSLTTKAVLLVRRAFQNS	11117
B39:	PRSTPSLTTKAVLLVAKFQNS	10786
B40:	PRSTPSLTTKAVLLARKFQNS	4542
B41:	PRSTPSLTTKAVLAVRKFQNS	3758
B42:	PRSTPSLTTKAVALVRKFQNS	3838
B43:	PRSTPSLTTKAALLVRKFQNS	7157
B44:	PRSTPSLTTAAVLLVRKFQNS	19499
B45:	PRSTPSLTAKAVLLVRKFQNS	7487
B46:	PRSTPSLATKAVLLVRKFQNS	7685
B47:	PRSTPSATTKAVLLVRKFQNS	8566

These data indicate that the sequence VLLV is a critical binding region within domain II, that domain II is preferably flanked on the amino-terminus by an amino acid sequence R¹¹-X-, wherein R¹¹ is a synthetic or naturally-occurring amino acid residue that is neutral or acidic under physiological conditions and X is any amino acid residue. More preferably, the sequence includes LTTR¹¹XVLLV, wherein X can optionally be alaninyl.

10 Additionally, these data indicate that the sequence VLLV is preferably flanked on the carboxyl-terminus by a pharmaceutically acceptable substituent equivalent in size to 1 to 3 amino acid residues, or more preferably, by 4 to 6 amino acid residues.

15

Example 3

This example provides data identifying the critical binding regions of domain III, as well as which residues

within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 receptor within domain III.

5	<u>Peptide Identifier</u>	<u>Peptide Sequence</u>	<u>Counts/minute bound</u>
	C1:	SSFYRLRFELRYRAERSKTFT	14571
	C2:	SSFYRLRFELRYRAERSKTF	13763
	C3:	SSFYRLRFELRYRAERSKT	8210
	C4:	SSFYRLRFELRYRAERSK	7619
	C5:	SSFYRLRFELRYRAERS	4707
	C6:	SSFYRLRFELRYRAER	2653
	C7:	SSFYRLRFELRYRAE	1821
	C8:	SSFYRLRFELRYRA	2509
	C9:	SSFYRLRFELRYR	2173
	C10:	SSFYRLRFELRY	1354
	C11:	SSFYRLRFELR	1127
	C12:	SSFYRLRFEL	1031
	C13:	SSFYRLRF	1019
	C14:	SSFYRLRF	952
	C15:	SSFYRLR	991
	C16:	SSFYRL	865
	C17:	SSFYRLRFELRYRAERSKTFT	15127
	C18:	SFYRLRFELRYRAERSKTFT	12750
	C19:	FYRLRFELRYRAERSKTFT	10136
	C20:	YRLRFELRYRAERSKTFT	7574
	C21:	RLRFELRYRAERSKTFT	5991
	C22:	LRFELRYRAERSKTFT	9610
	C23:	RFELRYRAERSKTFT	5307
	C24:	FELRYRAERSKTFT	5113
	C25:	ELRYRAERSKTFT	2204
	C26:	LYRAERSKTFT	6382
	C27:	RYRAERSKTFT	3150
	C28:	YRAERSKTFT	2401
	C29:	RAERSKTFT	1432
	C30:	AERSKTFT	1202
	C31:	ERSKTFT	1033
	C32:	RSKTFT	1345
	C33:	SSFYRLRFELRYRAERSKTFT	14610
	C34:	SSFYRLRFELRYRAERSKTFA	16952
	C35:	SSFYRLRFELRYRAERSKTAT	14809
	C36:	SSFYRLRFELRYRAERSKAFT	15011
	C37:	SSFYRLRFELRYRAERSATFT	7223
	C38:	SSFYRLRFELRYRAERA RA KTFT	12308

C39:	SSFYRLRFELRYRAE <u>ASKTFT</u>	3430
C40:	SSFYRLRFELRYRA <u>ARSKTFT</u>	17299
C41:	SSFYRLRFELRY <u>AAERSKTFT</u>	6743
C42:	SSFYRLRFELR <u>ARAERSKTFT</u>	17461
C43:	SSFYRLRFEL <u>AYRAERSKTFT</u>	7548
C44:	SSFYRLRF <u>EARYRAERSKTFT</u>	14120
C45:	SSFYRLRF <u>ALRYRAERSKTFT</u>	26802
C46:	SSFYRL <u>RAELRYRAERSKTFT</u>	13395
C47:	SSFYRL <u>AELRYRAERSKTFT</u>	9762

These data indicate that the sequence LRYRAERS is a critical binding region within domain III, that domain III is preferably flanked on the amino-terminus by an 5 amino acid residue R²¹, wherein R²¹ is a synthetic or naturally-occurring amino acid residue that has a side-chain that is neutral or basic under physiological conditions. Additionally, these data show that any of the amino acid residues of the critical binding domain 10 can be replaced, preferably by a conservative substitution, and that the arginanyl residues of the critical binding region are most important to the binding of the peptide. Moreover, while not meaning to be bound by any particular theory, it is apparent that this region 15 of the protein exists in a pleated-sheet motif. Accordingly, substitutions of amino acid residues by structure-breaking amino acid residues, e.g., prolinyl, is less preferred.

20 Example 4

This example provides data identifying the critical binding regions of domain IV, as well as which residues within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 25 receptor within domain IV. In the following tabulation

of data, rows D1-D10 were examined in one experiment, and rows D11-D57 were examined in a separate experiment. Thus, the numerical data obtained from rows D1-D10 should not be directly compared to the numerical data from rows 5 D11-D57.

<u>Peptide Identifier</u>	<u>Peptide Sequence</u>	<u>Counts/minute bound</u>
D1:	ATSLPVQDSSSVPLPTFLVAG	3995
D2:	VQDSSSVPLPTFLVAGGSLAF	4521
D3:	SVPLPTFLVAGGSLAFGTLLC	19756
D4:	TFLVAGGSLAFGTLLCIAIVL	32022
D5:	GGSLAFGTLLCIAIVLRFKKT	159174
D6:	FGTLLCIAIVLRFKKTWKLRA	143540
D7:	CIAIVLRFKKTWKLRALKEGK	52538
D8:	LRFKKTWKLRALKEGKTSMHP	20399
D9:	TWKLRALKEGKTSMHPYSLG	5530
D10:	ALKEGKTSMHPYSLGQLVPE	4969
D11:	GGSLAFGTLLCIAIVLRFKKT	20349
D12:	GGSLAFGTLLCIAIVLRFKK	18081
D13:	GGSLAFGTLLCIAIVLRFK	16082
D14:	GGSLAFGTLLCIAIVLRF	7694
D15:	GGSLAFGTLLCIAIVL	3948
D16:	GGSLAFGTLLCIAIVL	2456
D17:	GGSLAFGTLLCIAIV	1344
D18:	GGSLAFGTLLCIAI	1175
D19:	GGSLAFGTLLCIA	1153
D20:	GGSLAFGTLLCI	1202
D21:	GGSLAFGTLLC	1108
D22:	GGSLAFGTLL	1001
D23:	GGSLAFGTLL	997
D24:	GGSLAFGT	981
D25:	GGSLAFG	952
D26:	GGSLAF	1047
D27:	GGSLAFGTLLCIAIVLRFKKT	21945
D28:	GSLAFGTLLCIAIVLRFKKT	26441
D29:	SLAFGTLLCIAIVLRFKKT	24724
D30:	LAFGTLLCIAIVLRFKKT	22737
D31:	AFGTLLCIAIVLRFKKT	24047
D32:	FGTLLCIAIVLRFKKT	21799

D33:	GTLLCIAIVLRFKKT	15730
D34:	TLLCIAIVLRFKKT	12412
D35:	LLCIAIVLRFKKT	15510
D36:	LCIAIVLRFKKT	12422
D37:	CIAIVLRFKKT	8352
D38:	IAIVLRFKKT	6800
D39:	AIIVLRFKKT	4879
D40:	IVLRFKKT	4452
D41:	VLRFKKT	2551
D42:	LRFKKT	1958
D43:	GGSLAFGTLLCIAIVLRFKKT	20385
D44:	GGSLAFGTLLCIAIVLRFKK <u>A</u>	21366
D45:	GGSLAFGTLLCIAIVLRF <u>KAT</u>	28625
D46:	GGSLAFGTLLCIAIVLRF <u>AKT</u>	30792
D47:	GGSLAFGTLLCIAIVL <u>RAKKT</u>	20934
D48:	GGSLAFGTLLCIAIVL <u>AFKKT</u>	29450
D49:	GGSLAFGTLLCIAIV <u>ARFKKT</u>	22065
D50:	GGSLAFGTLLCIA <u>IAALRFKKT</u>	17857
D51:	GGSLAFGTLL <u>CIAAVLRFKKT</u>	28461
D52:	GGSLAFGTLL <u>CAAIVLRFKKT</u>	27699
D53:	GGSLAFGT <u>LLAIAIVLRFKKT</u>	34879
D54:	GGSLAFGT <u>LACIAIVLRFKKT</u>	22037
D55:	GGSLAFGT <u>ALCIAIVLRFKKT</u>	22123
D56:	GGSLAFG <u>ALLCIAIVLRFKKT</u>	22973
D57:	GGSLAFAT <u>LLCIAIVLRFKKT</u>	22324

These data indicate that the sequence IAIVLRF is a critical binding region within domain IV, that this critical binding domain is preferably flanked on the carboxyl-terminus by one or two lysinyl residues, or at least a pharmaceutically acceptable substituent comparable in size to one to three amino acid residues, which are -KKT in the sequence of the human IL-6 receptor. These data also show that the sequence is preferably flanked on the amino-terminus by a pharmaceutically acceptable substituent comparable in size to one, two, three, four, five, or six or more amino

acid residues. Of course, the pharmaceutically acceptable substituents could be synthetic or naturally-occurring amino acid residues. Moreover, the data show that any one of the amino acid residues can be replaced 5 by an alaninyl residue, resulting in an increase in affinity for IL-6. One skilled in the art will also appreciate that multiple (e.g., two or three) substitutions can be made in the critical binding region, and that when multiple replacements or substitutions are 10 made, then the substitutions are preferably conservatively selected. Additionally, the skilled artisan will note that the critical amino acid sequence IAIIVLRF resides in an extended region that has high affinity for the IL-6 ligand and that four of the seven 15 amino acid residues of this critical region can be found at either the amino- or carboxyl terminus of a polypeptide comprising the sequence.

Example 5

20 This example employs essentially the same techniques as Examples 1-4 except that fragments of the β -chain of the IL-6 receptor are used. As is known in the art, the β -chain is shared by multiple receptors. Thus, the identified fragments here are effective inhibitors of a 25 multiplicity of binding reactions in addition to the IL-6 ligand:IL-6 receptor interaction.

<u>Peptide Identifier</u>	<u>Peptide Sequence</u>	<u>Counts/minute bound</u>
E1:	MLTLQTWVWQALFIFLTTESTGEL	3365
E2:	ALFIFLTTESTGELLDPCGYISPE	1531
E3:	TGELLDPCGYISPEPESPVVQLHSNF	1300
E4:	ISPESPVVQLHSNFTAVCVLKEKC	1499

E5:	HSNFTAVCVLKEKCMDYFHVNANY	1292
E6:	KEKCMDYFHVNANYIVWKTNHFTI	1443
E7:	NANYIVWKTNHFTIIPKEQYTIINR	1327
E8:	HFTIPKEQYTIINRTASSVTFTDI	1143
E9:	IINRTASSVTFTDIASLNIQLTCN	1628
E10:	FTDIASLNIQLTCNILTGFQLEQN	3376
E11:	LTCNILTGFQLEQN VY GITIISGL	1816
E12:	LEQN VY GITIISGLPPEKPKNLSC	1669
E13:	ISGLPPEKPKNLSCIVNEGKKMRC	1202
E14:	NLSCIVNEGKKMRC EWDGGRETHL	1171
E15:	KMRCEWDGGRETHLETNFTLKSEW	1573
E16:	ETHLETNFTLKSEWATHKFADCKA	1035
E17:	KSEWATHKFADCKAKRDPTSTV	1409
E18:	DCKAKRDPTSTV DYSTVYFVNI	1548
E19:	SCTVDYSTVYFVNIEVWVEAENAL	3317
E20:	FVNIEVWVEAENALGKVTS DHINF	1413
E21:	ENALGKVTS DHINF D PVYKVKP NP	1122
E22:	HINF D PVYKVKP NP PHNL SVINSE	1728
E23:	KPNPPHNL SVINSEELSSILKLTW	1414
E24:	INSEELSSILKLTWTNPSIKSVII	1007
E25:	<u>KLTWTNPSIKSVII</u> <u>LKYNIQYRTK</u>	10331
E26:	SVIILKYNIQYRTK DASTWSQIPP	2832
E27:	YRTK DASTWSQIPP D TASTRSSF	1162
E28:	QIPP D TASTRSSF TVQDLKPFTE	1202
E29:	RSSFTVQDLKPFTEYVFRIRCMKE	1318
E30:	PFTEYVFRIRCMKEDGKG YWSDWS	1263
E31:	CMKEDGKG YWSDWSEEASGITYED	1732
E32:	SDWSEEASGITYEDRPSKAPSFWY	1161
E33:	TYEDRPSKAPSFWYKIDPSHTQGY	1215
E34:	SFWYKIDPSHTQGYRTVQLWKT	1145
E35:	TQGYRTVQLWKTLPFEEANGKIL	1169
E36:	WKTLPFEEANGKILDYEVTLTRWK	1465
E37:	GKILDYEVTLTRWKSHLQNYTVNA	1791
E38:	<u>TRWKSHLQNYTVNA</u> <u>T KLTVNLTND</u>	3652
E39:	<u>TVNATKLTVNLTND</u> <u>RYLATLTVRN</u>	4360
E40:	<u>LTND</u> <u>RYLATLTVRN</u> <u>LVGKSDAAVL</u>	4802
E41:	TVRNLVGKSDAAVLTIPACDFQAT	1104
E42:	AAVLTI PACDFQATHPVMDLKAFP	1121
E43:	FQATHPVMDLKAFPKDNMLWVEWT	1299
E44:	KAFPKDNMLWVEWTTPRESVKKYI	1175
E45:	VEWTTTPRESVKKYFILEWCVLSDKA	1389

E46:	KKYILEWCVLSDKAPCITDWQQED	1712
E47:	SDKAPCITDWQQEDGTVHRTYLRG	2079
E48:	QQEDGTVHRTYLRGNLAESKCYLI	1082
E49:	YLRGNLAESKCYLITVTPVYADGP	1541
E50:	CYLITVTPVYADGPGSPESIKAYL	1259
E51:	ADGPGSPESIKAYLKQAPPSKGPT	1194
E52:	KAYLKQAPPSKGPTVRTKKVKGNE	1816
E53:	KGPTVRTKKVKGNEAVLEWDQLPV	1636
E54:	GKNEAVLEWDQLPVDVQNGFIRNY	1307
E55:	<u>OLPVDVONGFIRNYTIFYRTIIGN</u>	4355
E56:	IRNYTIFYRTIIGNETAVNVDSSH	1635
E57:	IIGNETAVNVDSSHTEYTLSSLTS	1232
E58:	DSSHTEYTLSSLTSDEGKGDGP	1353
E59:	SLTSDTLYMVRMAAYTDEGGKDGP	1270
E60:	RMAAYTDEGGKDGPFTFTPKFA	1447
E61:	KDGPEFTFTTPKFAQGEIEAIVVP	1393
E62:	PKFAQGEIEAIVVPVCLAFLLTLL	2794
E63:	<u>IVVPVCLAFLLTLLGVLFCKNKR</u>	4519
E64:	<u>LTTLLGVLFCKNKRDLIKKHIWPN</u>	4501
E65:	<u>FNKRDLIKHHIWPNVPDPSKSHIA</u>	5741
E66:	IWPNVPDPSKSHIAQWSPTHPRH	1203
E67:	SHIAQWSPTHPRHNFNSKDQMY	1199
E68:	PPRHFNSKDQMYSDGNFTDVSVV	1231
E69:	QMYSDGNFTDVSVVIEANDKKPF	1194
E70:	VSVVEIEANDKKPFPEDLKSLDLF	1305
E71:	KKPFPEDLKSLDLFKKEKINTEGH	2694
E72:	LDLFKKEKINTEGHSSGIGGSSCM	1443
E73:	TEGHSSGIGGSSCMSSSRPSISSS	1060
E74:	SSCMSSSRPSISSSDENESSQNTS	1131
E75:	ISSSDENESSQNTSSTVQYSTVVH	1118
E76:	QNTSSTVQYSTVVHSGYRHQVPSV	1197
E77:	TVVHSGYRHQVPSVQVFSRSESTQ	1247
E78:	VPSVQVFSRSESTQPLLDSEERPE	1229
E79:	ESTQPLLDSEERPEDLQLVDHVDG	1384
E80:	ERPEDLQLVDHVDGGDGILPRQQY	1214
E81:	HVDGGDGILPRQQYFKQNCSQHES	1097
E82:	RQQYFKQNCSQHESSPDISHFERS	1087
E83:	QHESSPDISHFERSKQVSSVNEED	1250
E84:	FERSKQVSSVNEEDFVRLKQQISD	1015
E85:	NEEDFVRLKQQISDHISQSCGSGQ	1113
E86:	QISDHISQSCGSGQMKMFQEVSAA	1239

E87:	GSGQM KMFQE VSA ADA F GPG TEG Q	1001
E88:	VSA ADA F GPG TEG QVER FET VGM E	1091
E89:	TEG QVER FET VGM E AAT D E G M P K S	1131
E90:	VGM E AAT D E G M P K S Y L P Q T V R Q G G	1385
E91:	M P K S Y L P Q T V R Q G G Y M P Q	1226

These data demonstrate that the sequence SVIILKYNIQY is sufficient to bind to IL-6 ligand; however, better binding can be obtained by a sequence comprising the 5 sequence PSIKSVIILKYNIQY and the sequence can optionally comprise either WTNPSIKSVIILKYNIQY or even KLTWTNPSIKSVIILKYNIQY.

These data also indicate that the sequence TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL comprises a 10 multiplicity of subsequences, each of which can bind with IL-6 ligand. Similarly, QLPVDVQNGFIRNYTIFYRTIIGN comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand. Additionally, the sequence IVVPVCLAFLLTLLGVLFCFNKRDLIKKHIWPVNVPDPSKSHIA comprises a 15 multiplicity of subsequences, each of which can bind with IL-6 ligand.

For example, one skilled in the art will appreciate that any segment of the foregoing sequences comprising about six, twelve, eighteen, or twenty-four amino acid 20 residues is expected to bind with IL-6 ligand. Moreover, these data indicate to the skilled artisan that a multiplicity of amino acid substitutions, particularly conservative amino acid substitutions, within any of the above-described polypeptides can yield additional 25 polypeptides having a substantial ability to bind with IL-6 ligand and to inhibit the binding of IL-6 ligand to

IL-6 receptor and thereby inhibit IL-6 signaling under physiological conditions.

All publications cited herein are hereby
5 incorporated by reference to the same extent as if each publication were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

While this invention has been described with an
10 emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred polypeptides, nucleic acids, compositions and methods, and the like can be used and that it is intended that the invention can be practiced otherwise
15 than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WHAT IS CLAIMED IS:

1. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions and has the formula $R^1R^2R^3L^1L^2L^3R^4R^5$, and pharmaceutically acceptable salts thereof, wherein
 - 10 R^1 does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α -chain of the IL-6 receptor and is not linked to the moiety $-R^1R^2L^1L^2L^3R^4$ via a glycanyl residue or via a propionyl residue and is selected from the group consisting of hydrogen, $R^3C(O)-$, and R^3 ;
 - 15 R^2 is independently selected from the group consisting of arginanyl, naturally-occurring arginanyl equivalents, and synthetic arginanyl equivalents;
 - 20 L^1 is independently selected from the group consisting of leucanyl, naturally-occurring leucanyl equivalents, and synthetic leucanyl equivalents;
 - 25 R^3 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $-NHR^3$, and R^3 ; and
 - 30 R^4 is a pharmaceutically acceptable substituent group.
- 25 2. The polypeptide of claim 1, wherein R^2 is independently selected from the group consisting of arginanyl and lysinyl.
- 30 3. The polypeptide of claim 1, wherein R^2 is arginanyl.

4. The polypeptide of any of claims 1-3, wherein L' is independently selected from the group consisting of leucinyl, isoleucinyl, and valinyl.

5 5. The polypeptide of any of claims 1-3, wherein L' is leucinyl.

6. The polypeptide of any of claims 1-5, wherein R³ is R⁴, and

10 R⁴ is independently selected from the group consisting of a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R³ groups that are cyclic comprise from 0 to 2 atoms per 15 carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur,

any of the foregoing R⁴ groups can be substituted by one to about six substituents, which can be the same or 20 different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a 25 C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

7. The polypeptide of claim 1, wherein said polypeptide is RRLLLLR, wherein R is arginanyl and L is 30 leucinyl.

8. The polypeptide of any of claims 1-6, wherein R^2 is a -(serinyl-valinyl- R^5), and R^5 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 98 amino acid residues, -NHR⁴, and R⁴, and

5 R⁴ is independently selected from the group consisting of a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R³ groups that are cyclic comprise from 0 to 2 atoms per 10 carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur,

any of the foregoing R⁴ groups can be substituted by one to about six substituents, which can be the same or 15 different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a 20 C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

9. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological 25 conditions and has the formula R¹⁰R¹¹XVL¹²L¹²VR¹², and pharmaceutically acceptable salts thereof, wherein

R¹⁰ is a pharmaceutically acceptable substituent;

R¹¹ is selected from the group consisting of synthetic and naturally-occurring amino acid residues 30 having an acidic or neutral side-chain under physiological conditions;

X is any synthetic or naturally-occurring amino acid residue;

V is valinyl;

L² is leucinyl or isoleucinyl; and

5 R¹² is a pharmaceutically acceptable substituent.

10. A polypeptide of claim 9, wherein X is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or 10 neutral side-chain under physiological conditions.

11. A polypeptide of claim 9 or 10, wherein L² is leucinyl.

15 12. A polypeptide of any of claims 9-11, wherein R¹² is R¹³-R¹⁴;

16 R¹³ is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under 20 physiological conditions; and

R¹⁴ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR¹⁵, and R¹⁵; and

25 R¹⁵ is a pharmaceutically acceptable substituent group.

13. The polypeptide of any of claims 9-12, wherein R¹³ is selected from the group consisting of naturally-occurring amino acid residues having a side-30 chain that is acidic or neutral under physiological conditions.

14. The polypeptide of any of claims 9-13, wherein R¹³ is selected from the group consisting of synthetic and naturally-occurring amino acid residues 5 having a side-chain consisting of a C₁-C₆ straight-chain or branched alkyl moiety.

15. The polypeptide of claim 12, wherein R¹³ is alaninyl.

10

16. The polypeptide of any of claims 9-15, wherein R¹⁵ is R¹⁶, and

R¹⁶ is selected from the group consisting of hydrogen, a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, 15 a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R¹⁶ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, 20 and sulfur, and

any of the foregoing R¹⁶ groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate 25 moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

30

17. The polypeptide of any of claims 9-16, wherein R¹⁰ is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, R¹⁷C(O)-, and R¹⁷; and

5 R¹⁷ is a pharmaceutically acceptable substituent group.

18. The polypeptide of claim 17, wherein R¹⁷ is selected from the group consisting of hydrogen, a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, and a C₃-C₁₈ cycloalkyl, wherein any of the foregoing R¹⁷ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group

15 consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R¹⁷ groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

25

19. The polypeptide of claim 17, wherein R¹⁷ is hydrogen.

20. A polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions having the formula $R^{20}R^{21}L^*R^*Y^*R^*A^*E^*R^*S^*R^{22}$, wherein

5 R^{20} and R^{22} are pharmaceutically acceptable substituents;

R^{21} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions;

10 L^* , Y^* , E^* , and S^* are each independently selected from the group consisting of synthetic or naturally-occurring amino acid residues;

15 R^* is independently selected from the group consisting of synthetic or naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions; and

20 A^* is selected from the group consisting of alaninyl, glycanyl, isoleucanyl, leucanyl, valanyl, norleucanyl, norvalanyl, sarcosanyl, β -alaninyl, and α -aminoisobutyryl.

21. The polypeptide of claim 20, wherein R^{20} is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, and

25 $R^{23}C(O)-$, and R^{23} ; and wherein

30 R^{23} is selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{23} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which

can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur and

any of the foregoing R²³ groups can be substituted by one to about six substituents, which can be the same or

5 different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a

phosphamate moiety, a phosphate moiety, a phosphonate

moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a

10 C₁-C₈ monoalkylamine moiety, a C₁-C₈ dialkylamine moiety, and a C₁-C₈ trialkylamine moiety.

22. The polypeptide of claim 20 or 21, wherein R²² is selected from the group consisting of a polypeptide of 15 from 1 to about 100 amino acid residues, hydrogen, -NHR²³, and R²³; and wherein

R²³ is selected from the group consisting of a C₁-C₁₈ alkyl, a C₂-C₁₈ alkenyl, a C₂-C₁₈ alkynyl, a C₆-C₁₈ aryl, a C₇-C₁₈ alkaryl, a C₇-C₁₈ aralkyl, a C₃-C₁₈ cycloalkyl,

20 wherein any of the foregoing R²³ groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R²³ groups can be substituted by 25 one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a

C_1 - C_8 monoalkylamine moiety, a C_1 - C_8 dialkylamine moiety, and a C_1 - C_8 trialkylamine moiety.

23. The polypeptide of any of claims 20-22, wherein
5 R^{21} is alaninyl.

24. The polypeptide of any of claims 20-23, wherein
 R' is argininy1.

10 25. The polypeptide of any of claims 20-24, wherein
 L' is isoleucinyl or leucinyl.

26. The polypeptide of claim 25, wherein L' is
leucinyl.

15 27. The polypeptide of any of claims 20-26, wherein
 Y' is selected from the group consisting of tyrosinyl,
phenylalaninyl, tryptophanyl, and α -aminoisobutyryl.

20 28. The polypeptide of any of claims 20-27, wherein
 Y' is tyrosinyl.

25 29. The polypeptide of any of claims 20-28, wherein
 E' is selected from the group consisting of synthetic and
naturally-occurring amino acid residues having an acidic
side-chain under physiological conditions.

30. The polypeptide of claim 29, wherein E' is
selected from the group consisting of glutamyl, aspartyl,
and γ -aminopentane-1,5-dioyl.

31. The polypeptide of claim 30, wherein E* is glutamyl.

32. The polypeptide of any of claims 20-31, wherein 5 A* is alaninyl, glycinyl, or valinyl.

33. The polypeptide of claim 32, wherein A* is alaninyl.

10 34. The polypeptide of any of claims 20-33, wherein S* is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl.

15 35. The polypeptide of claim 34, wherein S* is serinyl.

36. A polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under physiological conditions, wherein said sequence comprises 20 at least I'A'I'V'L'R'F',

wherein I', L', and V' are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C₁-C₆ straight-chain or branched alkyl moiety;

25 R' is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions;

A* is selected from the group consisting of alaninyl, 30 glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl,

norvalinyl, sarcosinyl, β -alaninyl, and α -aminoisobutyryl;

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and 5 α -aminoisobutyryl,

and wherein at least four of the seven substituents of I'A'I'V'L'R'F* are selected such that I* is isoleucinyl, A* is alaninyl, V* is valinyl, L* is leucinyl, R* is argininy, and F* is phenylalaninyl;

10 and said polypeptide comprises less than about 200 contiguous amino acid residues that have a sequence that is identical to an amino acid sequence of the α -chain of the IL-6 receptor.

15 37. The polypeptide of claim 36, wherein said sequence comprises IAIVLRFK.

20 38. The polypeptide of claim 36, wherein said sequence comprises at least IAIVLRFKXX in which X is any synthetic or naturally-occurring amino acid residue.

39. The polypeptide of claim 36, wherein said sequence comprises at least LLCIAIVLRFK.

25 40. The polypeptide of claim 36, wherein said sequence comprises at least FGTLLCIAIVLRFKKT.

30 41. The polypeptide of any of claims 36-40, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span

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of less than about 100 contiguous amino acid residues of the α -chain of the IL-6 receptor.

42. The polypeptide of claim 41, wherein said
5 polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span of less than about 30 contiguous amino acid residues of the α -chain of the IL-6 receptor.

10 43. The polypeptide of claim 42, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span of less than about 16 contiguous amino acid residues of the α -chain of the IL-6 receptor.

15 44. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue
20 sequence of the β -chain of the IL-6 receptor and comprises the sequence SVIILKYNIQY.

45. The polypeptide of claim 44, comprising the sequence PSIKSVIILKYNIQY.

25 46. The polypeptide of claim 44, comprising the sequence WTNPSIKSVIILKYNIQY.

30 47. The polypeptide of claim 44, comprising the sequence KLTWTNPSIKSVIILKYNIQY.

48. The polypeptide of any of claims 44-47, having up to about 100 contiguous amino acid residues that are identical to an amino acid residue sequence of the β -chain of the IL-6 receptor.

5

49. The polypeptide of any of claims 44-47, having up to about 50 contiguous amino acid residues that are identical to an amino acid residue sequence of the β -chain of the IL-6 receptor.

10

50. The polypeptide of any of claims 44-47 consisting of the recited sequence.

51. The polypeptide of any of claims 44-50 comprising from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue, and wherein the polypeptide inhibits the binding of human IL-6 ligand to human IL-6 receptor under physiological conditions.

52. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino residue sequence of the β -chain of the IL-6 receptor, and comprises a portion of the sequence TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL.

30 53. The polypeptide of claim 52, wherein said portion is about a 6-mer.

54. The polypeptide of claim 52, wherein said portion is about a 12-mer.

5 55. The polypeptide of claim 52, wherein said portion is about an 18-mer.

56. The polypeptide of claim 52, wherein said portion is about a 24-mer.

10

57. The polypeptide of any of claims 52-56, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β -chain of the IL-6 receptor.

15

58. The polypeptide of any of claims 52-57, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β -chain of the IL-6 receptor.

20

59. The polypeptide of any of claims 52-58, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-
25 occurring amino acid residue.

60. The polypeptide of any of claims 53-59, further comprising a pharmaceutically acceptable substituent.

30

61. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological

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conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β -chain of the IL-6 receptor, and comprises a portion of the sequence

5 QLPV DVQNGFIRNYTIFYRTIIGN.

62. The polypeptide of claim 61, wherein said portion is about a 6-mer.

10 63. The polypeptide of claim 61, wherein said portion is about a 12-mer.

64. The polypeptide of claim 61, wherein said portion is about an 18-mer.

15

65. The polypeptide of any of claims 61-64, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β -chain of the IL-6 receptor.

20

66. The polypeptide of any of claims 61-65, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β -chain of the IL-6 receptor.

25

67. The polypeptide of any of claims 61-66, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-
30 occurring amino acid residue.

70

68. The polypeptide of any of claims 61-67, further comprising a pharmaceutically acceptable substituent.

69. A polypeptide, which inhibits the binding of
5 IL-6 ligand with IL-6 receptor under physiological
conditions, comprises up to about 200 contiguous amino
acid residues that are identical to an amino acid residue
sequence of the β -chain of the IL-6 receptor, comprises a
portion of the sequence

10 IVVPVCLAFLLTLLGVLFCKFNKRDLIKKHIWPVNVPDPSKSHIA.

70. The polypeptide of claim 69, wherein said
portion is about a 6-mer.

15 71. The polypeptide of claim 69, wherein said
portion is about a 12-mer.

72. The polypeptide of claim 69, wherein said
portion is about an 18-mer.

20 73. The polypeptide of claim 69, wherein said
portion is about a 24-mer.

74. The polypeptide of any of claims 69-73, having
25 up to about 100 contiguous amino acid residues that have
an identical sequence to an amino acid residue sequence
of the β -chain of the IL-6 receptor.

75. The polypeptide of any of claims 69-73, having
30 up to about 50 contiguous amino acid residues that have

an identical sequence to an amino acid residue sequence of the β -chain of the IL-6 receptor.

76. The polypeptide of any of claims 69-75, wherein
5 said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.

10 77. The polypeptide of any of claims 69-76, further comprising a pharmaceutically acceptable substituent.

78. The polypeptide of any of claims 1-77, wherein
said polypeptide consists of naturally-occurring amino
15 acid residues.

79. A nucleic acid that encodes the polypeptide of any of claims 1-78 and can be expressed in a cell.

20 80. The nucleic acid of claim 79, in which the nucleic acid encoding the polypeptide is operably linked to a signal sequence, wherein said signal sequence is translated as a fusion protein with the polypeptide to form a signal sequence-polypeptide fusion, and wherein
25 said signal sequence can cause secretion of at least the polypeptide by a cell in which the nucleic acid is expressed.

81. A composition comprising the polypeptide of any
30 of claims 1-78 or a nucleic acid of claim 79 or 80 and a carrier therefor.

82. The composition of claim 81, wherein said composition comprises an agent or substituent that increases the solubility of the polypeptide.

5

83. The composition of claim 82, wherein said agent that increases the solubility of the polypeptide is a liposome.

10

84. The composition of claim 82, wherein said substituent is a saccharide.

15

85. A composition comprising a solid support matrix to which is attached a polypeptide of any of claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLLR, RXVLLV, LRYRAERS, IAIIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY,

20

TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLTLLGVLFCKNKRDLIKKHIWPNVPDPSKSHIA.

25

86. A method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, which method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of a polypeptide of any of claims 1-78, a nucleic acid of claim 79 or 80, or an antibody to a polypeptide of any of 30 claims 1-78.

87. A method of removing IL-6 ligand from a bodily fluid of a mammal, which method comprises extra-corporeally contacting said bodily fluid with a solid support to which is attached a polypeptide of any of 5 claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSIVIILKYNIQY, or a portion of any of the following polypeptides:
WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY,
10 TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL,
QLPVDVQNGFIRNYTIFYRTIIGN, and
IVVPVCLAFILLTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

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		Formula	MW
E-2560	H-Val-OH	C ₅ H ₁₁ NO ₂	117.15
E-3250	H-[¹⁵ N]Val-OH	C ₅ H ₁₁ ¹⁵ NO ₂	118.15
F-2180	H-D-Val-OH	C ₅ H ₁₁ NO ₂	117.15
F-3025	H-DL-Val-OH	C ₅ H ₁₁ NO ₂	117.15
E-3S10	H-Val-ally ester p-tosylate	C ₈ H ₁₆ NO ₂ · C ₇ H ₈ O ₃ S	330.43
E-2565	H-Val-NH ₂ · HBr	C ₅ H ₁₂ N ₂ O · HBr	197.08
E-2570	H-Val-NH ₂ · HCl	C ₅ H ₁₂ N ₂ O · HCl	152.63
E-2585	H-Val-NHtBu	C ₉ H ₂₀ N ₂ O	172.27
E-2600	H-Val-p-nitrobenzyl ester · HBr	C ₁₂ H ₁₆ N ₂ O ₄ · HBr	333.19
E-2590	H-Val-OtBu · HCl	C ₉ H ₁₉ NO ₂ · HCl	209.72
F-3170	H-D-Val-OtBu · HCl	C ₉ H ₁₉ NO ₂ · HCl	209.72
E-2575	H-Val-OBzL · HCl	C ₁₂ H ₁₂ NO ₂ · HCl	243.74
E-2580	H-Val-OBzL · p-tosylate	C ₁₂ H ₁₇ NO ₂ · C ₇ H ₈ O ₃ S	379.48
F-3500	H-D-Val-OBzL · p-tosylate	C ₁₂ H ₁₇ NO ₂ · C ₇ H ₈ O ₃ S	379.48
E-1825	H-Val-OEt · HCl	C ₇ H ₁₅ NO ₂ · HCl	181.65
E-2595	H-Val-OMe · HCl	C ₆ H ₁₃ NO ₂ · HCl	167.64
F-3160	H-D-Val-OMe · HCl	C ₆ H ₁₃ NO ₂ · HCl	167.64
C-3700	Z-N-Me-Val-OH	C ₁₄ H ₁₉ NO ₄	265.31
C-2805	Z-Val-OH	C ₁₃ H ₁₇ NO ₄	251.28
C-2810	Z-D-Val-OH	C ₁₃ H ₁₇ NO ₄	251.28
C-2815	Z-Val-NHtBu	C ₁₂ H ₂₆ N ₂ O ₃	306.41
C-2830	Z-Val-ONp	C ₁₉ H ₂₀ N ₂ O ₄	372.38
C-2820	Z-Val-OSu	C ₁₇ H ₂₀ N ₂ O ₄	348.36
C-2825	Z-D-Val-OSu	C ₁₇ H ₂₀ N ₂ O ₄	348.36

Fig. 1

Special Amino Acids and Amino Acid Derivatives

F-1190	H-Abu-OH
F-2440	H-Abu-NH ₂ · HCl
F-3035	H-Abu-OtBu · HCl
F-3755	H- γ -Abu-OtBu · HCl
E-2660	Ac-p-aminohippuric acid
F-1015	Ac-p-amino-Phe-OMe
F-2275	Ac-p-bromo-DL-Phe-OH
F-3265	Ac-p-Bz-D-Phe-OH [Ac-D-Bpa-OH]
M-1935	Ac-Cys(farnesyl)-OH
F-2930	Ac-Cys(farnesyl)-OMe
F-1020	Ac-Dob(Boc)-OH
F-3175	Ac-4,5 dehydro-Leu-OH
F-1030	Ac-3,5-dinitro-Tyr-OEt
F-1010	DL-2-Acetylamino-6-N-Boc-amino-4-hexynoic acid · DCHA
F-2295	Ac-p-fluoro-DL-Phe-OH
F-3015	Ac-p-iodo-D-Phe-OH
F-2940	Ac-Met(O)-OH
F-2305	Ac-5-Me-DL-Trp-OH
F-2420	Ac-D-2-Nal-OH
F-1080	Ac-DL-propargyl-Gly-OEt
E-3060	H-Aib-OtBu
F-1160	H-allo-Ile-OH
F-1165	H-D-allo-Ile-OH
F-1170	H-DL-allo-Ile-OH



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F-1175	H-allo-Thr-OH
F-1180	H-D-allo-Thr-OH
F-2635	H-DL-allo-Thr-OH
F-2545	H-allo-Thr-OMe · HCl
F-2540	H-allo-Thr(tBu)-OH
F-2560	L- α -Aminoadipic acid [L-2-Aminohexanedioic acid]
F-2575	D- α -Aminoadipic acid [D-2-Aminohexanedioic acid]
F-1185	DL- α -Aminoadipic acid [DL-2-Aminohexanedioic acid]
F-3150	L-2-Aminoadipic acid- δ -2-butyl ester [L-2-Aminohexanedioic acid- δ -2-butyl ester]
F-3130	L- α -Aminoadipic acid- δ -methyl ester · HCl [L-2-Aminohexanedioic acid- δ -methyl ester · HCl]
F-3800	1-Aminocyclopropane-1-carbohydroxamic acid · HCl
F-3805	1-Aminocyclopropane-1-carboxylic acid
F-1200	H-4-Amino-3,5-diodo-Phe-OH
F-1205	7-Aminoheptanoic acid
F-3480	4-Amino-1-methylimidazole-2-carboxylic acid-ethyl ester · HCl
F-3485	4-Amino-1-methylpyrrole-2-carboxylic acid methyl ester · HCl
F-1225	H-p-Amino-Phe-OH · HCl
F-2855	H-p-Amino-D-Phe-OH · HCl
F-1230	H-p-Amino-DL-Phe-OH
F-1235	DL- α -Aminopimelic acid [DL-2-Aminoheptanedioic acid]
H-3605	4-Aminopiperidine-4-carboxylic acid [H-Pip-OH]
F-2740	L-2-Aminosuberic acid [L-2-Aminoctanedioic acid/H-Asu-OH]

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F-3315	D-a-Aminosuberic acid [D-2-Aminooctanedioic acid/H-D-Asu-OH]
F-3305	DL- α -Aminosuberic acid [DL-2-Aminooctanedioic acid/H-DL-Asu-OH]
F3675	H-3-Amino-Tyr-OH • 2 HCl [5-Aminopentanoic acid-benzyl ester • p-tosylate]
E-1700	n-Aminovaleric acid-benzyl ester • p-tosylate [5-Aminopentanoic acid-benzyl ester • p-tosylate]
F-1281	L-Azetidine-2-carboxylic acid
F-2285	Azetidine-3-carboxylic acid
F3075	H-p-Azido-Phe-OH
F-2490	H- β -(3-Benzothienyl)-Ala-OH
F-2485	H- β -(3-Benzothienyl)-D-Ala-OH
F-1215	Bestatin [(2S,3R)-3Amino-2-hydroxy-4-phenylbutanoyl-L-leucine]
F-2630	S-[2,3-Bis(palmitoyloxy)-(2RS)-propyl]-N-palmitoyl-(R)-Cys-OH
A-1135	Boc-Abu-OH
A-1175	Boc-D-Abu-OH
A-1140	Boc- γ -Abu-OH
A-1145	Boc-Abu-ONp
A-3240	Boc-Abz-OH
A-2800	Boc-4-Abz-OH
A-4300	Boc-4-Abz-Osu
A2015	Boc-Aib-OH
A3825	Boc-Aib-Osu
A-3345	Boc-allo-Ile-OH
A-3735	Boc-D-allo-Ile-OH
A-1150	Boc- ϵ -aminocaproic acid
A-1155	Boc- ϵ -aminocaproic acid-Osu

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A-1160	Boc-4-amino-3,5-diiodo-Phe-OH
A-1175	Boc-7-aminoheptanoic acid
A-1185	Boc-p-amino-Phe-OH
A-2980	Boc-p-amino-D-Phe-OH
A-3975	Boc-p-amino-Phe(Fmoc)-OH
A-4065	Boc-p-amino-D-Phe(Fmoc)-OH
A-1455	Boc-p-amino-Phe(Z)-OH
A-4370	1-Boc-4-aminopiperidine-4-carboxylic acid [H-Pip(Boc)-OH]
A-3310	Boc-11-aminoundecanoic acid
A-3405	Boc- $\ddot{\sigma}$ -aminovaleric acid [Boc-5-aminopentanoic acid]
A-3S70	Boc-p-azido-Phe-OH
A-4200	Boc-p-azido-D-Phe-OH
A-3540	Boc- β -(3-benzothienyl)-Ala-OH
A-3695	Boc-p-bromo-Phe-OH
A-4205	Boc-p-bromo-D-Phe-OH
A-4490	Boc-p-tBu-Phe-OH
A-4485	Boc-p-tBu-D-Phe-OH
A-3295	Boc-p-Bz-Phe-OH [Boc-Bpa-OH]
A-3S60	Boc-p-Bz-D-Phe-OH [Boc-D-Bpa-OH]
A-4325	Boc-p-carboxy-Phe(OtBu)-OH • DCHA
A-3860	Boc- β -chloro-Ala-OH
A-1525	Boc-p-chloro-Phe-OH
A-2655	Boc-p-chloro-D-Phe-OH
A-1535	Boc- β -cyano-Ala-OH

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A-1540	Boc- β -cyano-D-Ala-OH
A-4375	Boc-p-cyano-Phe-OH
A-3760	Boc- β -cyclohexyl-Ala-OH
A-3840	Boc- β -cyclohexyl-D-Ala-OH
A-2960	Boc- β -cyclohexyl-Ala-OH • DCHA
A-2920	Boc- β -cyclohexyl-D-Ala-OH • DCHA
A-4465	Boc-cyclohexyl-Gly-OH
A-4470	Boc-cyclohexyl-D-Gly-OH
A-3340	N-Boc-cyclohexylstatine [N-Boc-(3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid]
A-4150	Boc- β -cyclopropyl-Ala-OH
A-3215	Boc-Dab-OH
A-4215	Boc-D-Dab-OH
A-4415	Boc-Dab-OtBu • HCl
A-4125	Boc-Dab-(Aloc)-OH
A-3480	Boc-Dab-(Boc)-OH • DCHA
A-3S20	Boc-Dab-(Fmoc)-OH
A-4230	Boc-D-Dab(Fmoc)-OH
A-2905	Boc-Dab(Z)-OH • DCHA
A-4260	Boc-D-Dab(Z)-OH • DCHA
A-3220	Boc-Dap-OH
A-3S90	Boc-D-Dap-OH
A-4115	Boc-Dap(Aloc)-OH
A-3475	Boc-Dap(Boc)-OH • DCHA
A-4130	Boc-Dap(bromoacetyl)-OH
A-4290	Boc-Dap(Dnp)-OH
A-4295	Boc-Dap(Dnp)-OSu

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A-3S80	Boc-Dap(Fmoc)-OH
A-4235	Boc-D-Dap(Fmoc)-OH
A-3000	Boc-Dap(Z)-OH · DCHA
A-4265	Boc-D-Dap(Z)-OH · DCHA
A-3485	Boc-4,5-dehydro-Leu-OH · DCHA
A-1550	Boc-3,4-dehydro-Pro-OH
A-1555	Boc-3,5-dibromo-Tyr-OH
A-4220	Boc-3,5-dibromo-D-Tyr-OH
A-4045	Boc-3,4-dichloro-D-Phe-OH
A-1580	Boc-3,5-diodo-Tyr-OH
A-4225	Boc-3,5-diodo-D-Tyr-OH
A-1590	Boc-3,5-diodo-Tyr-OMe
A-1585	Boc-3,5-diodo-Tyr-OSu
A-1410	Boc-3,5-diodo-Tyr(3'-bromo-Bzl)-OH
A-2570	Boc-3,5-diodo-Tyr(2',6'-dichloro-Bzl)-OH
A-3065	Boc-p-fluoro-Phe-OH
A-2835	Boc-p-fluoro-D-Phe-OH
A-1605	Boc-p-fluoro-DL-Phe-OH
A-4320	Boc- α -(Fmoc-amino)-Gly-OH [Fmoc- α -(Boc-amino) Gly-OH]
A-4040	Boc-Homoarg-OH · HCl
A-3775	Boc-Homoarg(Et) ₂ -OH
A-3780	Boc-D-Homarg(Et) ₂ -OH
A-3935	Boc-Homoarg(NO ₂)-OH
A-3465	Boc-Homocit-OH
A-2870	Boc-D-Homocit-OH
A-3420	Boc-Homocys(Mbzl)-OH

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A-4255	Boc-D-Homocys(Mbzl)-OH
A-3610	Boc-Homocys(Trt)-OH
A-1190	Boc-Homophe-OH
A-1195	Boc-D-Homophe-OH
A-2830	Boc-Homopro-OH
A-3125	Boc-D-Homopro-OH
A-4165	Boc-7-hydroxy-Tic-OH
A-4170	Boc-7-hydroxy-D-Tic-OH
A-1800	Boc-p-iodo-Phe-OH
A-3640	Boc-p-iodo-D-Phe-OH
A-1805	Boc-p-iodo-DL-Phe-OH
A-3815	Boc-isonipecotic acid [Boc-piperidine-4-carboxylic acid]
A-3715	Boc-N-Me-Abz-OH
A-2025	Boc-N-Me-allo-Ile-OH
A-3730	Boc-N-Me-D-allo-Ile-OH
A-2880	Boc-N-Me-p-chloro-D-Phe-OH
A-2070	Boc-N-Me-p-nitro-Phe-OH · DCHA
A-4495	Boc-p-Me-Phe-OH
A-4500	Boc-p-Me-D-Phe-OH
A-1965	Boc-Met(O)-OH
A-2885	Boc-Met(O ₂)-OH
A-4145	Boc- α -Me-DL-Val-OH
A-3225	Boc-1-Nal-OH
A-4305	Boc-D-1-Nal-OH
A-2850	Boc-2-Nal-OH
A-2575	Boc-D-2-Nal-OH

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A-3110 Boc-Neopentylgly-OH
A-4210 Boc-D-Neopentylgly-OH
A-2125 Boc-p-nitro-Phe-OH
A-2130 Boc-p-nitro-D-Phe-OH
A-3645 Boc-Oic-OH
[Boc-L-octohydroindole-2-carboxylic acid]
A-2965 Boc-Pen(Acm)-OH
A-2970 Boc-D-Pen(Acm)-OH
A-3660 Boc-Pen(Mbzl)-OH · DCHA
A-3665 Boc-D-Pen(Mbzl)-OH · DCHA
A-2900 Boc-Pen(Mob)-OH
A-3990 Boc-D-Pen(Mob)-OH
A-3650 Boc-Pen(NPys)-OH
A-3655 Boc-D-Pen(NPys)-OH
A-3S50 Boc-Pen(Trt)-OH
A-3S55 Boc-D-Pen(Trt)-OH
A-3915 Boc-pentafluoro-Phe-OH
A-3960 Boc-pentafluoro-D-Phe-OH
A-4385 Boc-p-phenyl-Phe-OH
[Boc- β -(4-biphenyl)-Ala-OH; Boc-Bip-OH]
A-4390 Boc-p-phenyl-D-Phe-OH
[Boc- β -(4-biphenyl)-D-Ala-OH; Boc-D-Bip-OH]
A-4100 N-Boc-phenylstatine
[N-Boc-(3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid]
B-3115 1-Boc-piperidine-4-Fmoc-amino-4-carboxylic acid
[Fmoc-Pip(Boc)-OH]
A-3745 Boc- β -(3-pyridyl)-Ala-OH
A-2855 Boc- β -(3-pyridyl)-D-Ala-OH
A-4395 Boc- β -(2-quinolyl)-Ala-OH
A-4400 Boc- β -(2-quinolyl)-D-Ala-OH

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A-1180	N-Boc-statine [N-Boc-(3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid]
A-3945	Boc-L-thiazolidine-4-carboxylic acid [Boc-L-thioproline]
A-3940	Boc-D-thiazolidine-4-carboxylic acid [Boc-D-thioproline]
A-2290	Boc-β-(2-thienyl)-Ala-OH
A-2295	Boc-β-(2-thienyl)-D-Ala-OH
A-2300	Boc-β-(2-thienyl)-DL-Ala-OH
A-3700	Boc-L-thiocitrulline-OtBu
A-4360	Boc-Thionoala-1-(6-nitro)benzotriazolide
A-4345	Boc-Thionoleu-1-(6-nitro)benzotriazolide
A-4355	Boc-Thionophe-1-(6-nitro)benzotriazolide
A-4365	Boc-Thionoser(Bzl)-1-(6-nitro)benzotriazolide
A-4350	Boc-Thionoval-1-(6-nitro)benzolriazolide
A-3070	Boc-Tic-OH
A-3075	Boc-D-Tic-OH
A-4090	Boc-D-Tpi-OH [Boc-D-1,2,3,4-tetrahydronoharman-3-carboxylic acid]
F-1305	H-p-Bromo-Phe-OH
F-3700	H-p-Bromo-D-Phe-OH
F-1310	H-p-Bromo-DL-Phe-OH
F-3790	H-p-tBu-Phe-OH
F-3795	H-p-tBu-D-Phe-OH
F-3250	n-Butyloxycarbonyl-Dap-OH
F-2800	H-p-Bz-Phe-OH [H-Bpa-OH]
F-2810	H-p-Bz-D-Phe-OH [H-D-Bpa-OH]

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F-2345	Carbamoyl-DL-Ala-OH
F-1375	Carbamoyl-β-Ala-OH
M-2240	Carbamoyl-Asp-OH · magnesium salt
F-2430	Carbamoyl-Leu-OH
Q-1140	β-Carboline-3-carboxylic acid-ethyl ester
Q-1145	β-Carboline-3-carboxylic acid-propyl ester
F-3590	H-p-Carboxy-Phe-OH
F-3585	H-p-Carboxy-Phe(OtBu)-OH
F-2700	L-Carnitine [(R)-β-Hydroxy-γ-(trimethylammonio)butyrate]
F-1425	H-β-Chloro-Ala-OH
F-1430	H-β-Chloro-Ala-OH · HCl
F-1435	H-β-Chloro-D-Ala-OH · HCl
F-1440	H-β-Chloro-DL-Ala-OH
F-2325	H-β-Chloro-DL-Ala-OH · HCl
F-3380	H-β-Chloro-Ala-NHOH
F-3465	H-β-Chloro-Ala-OMe · HCl
F-1445	H-p-Chloro-Phe-OH
F-2520	H-p-Chloro-D-Phe-OH
F-1450	H-p-Chloro-DL-Phe-OH
F-2690	H-p-Chloro-D-Phe-OMe · HCl
F-1455	H-p-Chloro-DL-Phe-OMe · HCl
F-1460	H-β-Cyano-Ala-OH
F-3610	H-p-Cyano-Phe-OH
F-2500	H-β-Cyclohexyl-Ala-OH · HCl
F-2505	H-β-Cyclohexyl-D-Ala-OH · HCl
F-3760	H-Cyclohexyl-Gly-OH · salt
F-3765	H-Cyclohexyl-D-Gly-OH · salt

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F-2830	Cyclohexylstatine [(3S,4S)-4-Amino-5-cyclohexyl-3-hydroxypentanoic acid]
F-1470	H- β -(1-Cyclopentenyl)-DL-Ala-OH
F-1465	H- β -(1-Cyclopentenyl)-DL-Ala-OH
F-3470	H- β -Cyclopropyl-Ala-OH
F-1475	L-Cycloserine
F-1480	D-Cycloserine
F-1485	DL-Cycloserine
F-3050	H-Dob-OH · 2 HCl
F-3055	H-D-Dob-OH · 2 HCl
A-3305	H-Dob(Boc)-OH
E-3360	H-Dob(Boc)-OMe · HCl
F-3040	H-Dop-OH · HCl
F-3045	H-D-Dop-OH · HCl
F-3420	H-Dop(Boc)-OMe · HCl
F-2985	H-4,5-Dehydro-Leu-OH
F-2970	H-trans-4,5-Dehydro-Lys-OH [DL-trans-2,6-Diamino-4-hexenoic acid]
F-1490	H-3,4 Dehydro-Pro-OH
F-2705	H-3,4-Dehydro-DL-Pro-OH
F-1495	H-3,4-Dehydro-Pro-NH ₂ · HCl
F-1500	H-3,4-Dehydro-Pro-OMe · HCl
F-1505	2,6-Diaminopimelic (LL,DD and Meso) [2,6-Diaminoheptanedioic acid]
F-1510	H-6-Diazo-5-oxo-Nle-OH [L-DON]
F-2185	H-6-Diazo-5-oxo-D-Nle-OH [D-DON]

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F-1520	H-3,5-Dibromo-Tyr-OH
F-3395	H-3,4-Dichloro-Phe-OH
F-3400	H-3,4-Dichloro-D-Phe-OH
F-3695	H- β,β , Dicyclohexyl-DL-Ala-OH
F-2395	H- α -Difluoro-Me-DL-Orn-OH [DFMO]
F-1525	H- β -(3,4-Dihydroxyphenyl)-DL-Ser-OH [DL-Threo-DOPS]
F-3460	H-2,5-Diiodo-His-OH · HCL
F-2225	H-3,5-Diiodo-Tyr-OH
F-3005	H-3,5-Diiodo-D-Tyr-OH
E-2385	H-3,5-Diiodo-Tyr-OMe · HCL
M-1925	FA-Cys(farnesyl)-OH
M-1920	FA-Cys(farnesyl)-OMe
F-2530	H- β -Fluoro-DL-Ala-OH
F-3285	H-m-Fluoro-Phe-OH
F-3290	H-m-Fluoro-D-Phe-OH
F-2135	H-m-Fluoro-DL-Phe-OH
F-1530	H-p-Fluoro-Phe-OH
F-2320	H-p-Fluoro-D-Phe-OH
F-1535	H-p-Fluoro-DL-Phe-OH
F-3820	H-p-Fluoro-Phe-OEt · HCL
F-3295	H-m-Fluoro-D-Phe-OMe · HCL
F-1540	H-p-Fluoro-DL-Phe-OMe · HCL
B-1780	Fmoc-Abu-OH
B-2920	Fmoc-D-Abu-OH
B-1910	Fmoc- γ -Abu-OH

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B-3260	Fmoc-Abz-OH
B-2985	Fmoc-4-Abz-OH
B-1860	Fmoc-Aib-OH
B-2880	Fmoc-allo-Ile-OH
B-2230	Fmoc-D-allo-Ile-OH
B-3100	Fmoc-allo-Thr-OH
B-3090	Fmoc-D-allo-Thr-OH
B-1815	Fmoc-allo-Thr(tBu)-OH
B-1810	Fmoc-allo-Thr(tBu)-Odhbt
B-3280	Fmoc- α -allyl-DL-Gly-OH [Fmoc-DL-2-amino-4-pentanoic acid]
B-2440	Fmoc-L- α -amino adipic acid- δ -t-butyl ester [Fmoc-L-2-amino hexanedioic acid- δ -t-butyl ester]
B-1560	Fmoc- ϵ -aminocaproic acid
B-3310	2-(Fmoc-amino)-3-(2,2-dimethyl-4H-benzol[1,3]dioxin-6-yl)-propionic acid
B-2070	Fmoc-p-amino-Phe-OH
B-1995	Fmoc-p-amino-Phe-(Boc)-OH
B-2930	Fmoc-p-amino-D-Phe-(Boc)-OH
B-2360	Fmoc-p-azido-Phe-OH
B-2830	Fmoc- β -(3-benzothienyl)-Ala-OH
B-3320	Fmoc-p-tBu-Phe-OH
B-3325	Fmoc-p-tBu-D-Phe-OH
B-2220	Fmoc-p-Bz-Phe-OH [Fmoc-Bpa-OH]
B-2340	Fmoc-p-Bz-D-Phe-OH [Fmoc-D-Bpa-OH]
B-3070	Fmoc-p-carboxy-Phe(OtBu)-OH
B-2115	Fmoc-p-chloro-Phe-OH

B-1900	Fmoc-p-chloro-D-Phe-OH
B-3125	Fmoc-p-cyano-Phe-OH
B-1975	Fmoc-β-cyclohexyl-Ala-OH
B-2345	Fmoc-β-cyclohexyl-D-Ala-OH
B-3270	Fmoc-cyclohexyl-Gly-OH
B-3275	Fmoc-cyclohexyl-D-Gly-OH
B-2905	Fmoc-β-cyclopropyl-Ala-OH
B-3120	Fmoc-Cys(Boc-3-aminopropyl)-OH
B-2300	Fmoc-Dab-OH
B-2365	Fmoc-D-Dab-OH
B-2860	Fmoc-Dab-(Adpoc)-OH
B-2850	Fmoc-Dab-(aloc)-OH
B-1800	Fmoc-Dab-(Boc)-OH
B-2960	Fmoc-D-Dab(Boc)-OH
B-2270	Fmoc-D-Dab(Fmoc)-OH
B-3250	Fmoc-Dab(Z)-OH
B-2385	Fmoc-Dap-OH
B-3055	Fmoc-D-Dap-OH
B-2865	Fmoc-Dap(Adpoc)-OH
B-2845	Fmoc-Dap(Aloc)-OH
B-2380	Fmoc-Dap(Boc)-OH
B-2965	Fmoc-D-Dap(Boc)-OH
B-2995	Fmoc-Dap(Dnp)-OH
B-2265	Fmoc-Dap(Fmoc)-OH
B-2255	Fmoc-4,5-dehydro-Leu-OH
B-1660	Fmoc-3,4-dehydro-Pro-OH

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B-1275	Fmoc-3,5-dibromo-Tyr-OH
B-1285	Fmoc-3,5-Diiodo-Tyr-OH
B-3265	Fmoc-3,5,dinitro-Tyr-OH
B-2595	Fmoc-m-fluoro-Phe-OH
B-2835	Fmoc-p-fluoro-Phe-OH
B-3210	Fmoc-p-fluoro-D-Phe-OH
B-1550	Fmoc-p-fluoro-DL-Phe-OH
B-3130	Fmoc-Homoarg(Pmc)-OH
B-2250	Fmoc-Homocit-OH
B-2390	Fmoc-D-Homocit-OH
B-2405	Fmoc-Homocys(Trt)-OH
B-1535	Fmoc-Homophe-OH
B-2810	Fmoc-D-Homophe-OH
B-2285	Fmoc-Homopro-OH
B-2290	Fmoc-D-Homopro-OH
B-2750	Fmoc-p-iodo-Phe-OH
B-1740	Fmoc-3-iodo-Tyr-OH
B-3190	Fmoc-isonipecotic acid
B-2590	Fmoc-DL-Isoser-OH
B-3335	Fmoc-p-Me-Phe-OH
B-3330	Fmoc-p-Me-D-Phe-OH
B-2130	Fmoc-Met(O)-OH
B-1905	Fmoc-Met(O ₂)-OH
B-1965	Fmoc-1-Nal-OH
B-3020	Fmoc-D-1-Nal-OH
B-2100	Fmoc-2-Nal-OH

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B-1950 Fmoc-D-2-Nal-OH

B-2690 Fmoc-m-nitro-p-hydroxy-Phe-OH
[Fmoc-m-nitro-Tyr-OH]

B-1395 Fmoc-p-nitro-Phe-OH

B-2350 Fmoc-p-nitro-D-Phe-OH

B-2690 Fmoc-m-nitro-Tyr-OH
[Fmoc-m-nitro-p-hydroxy-Phe-OH]

B-2425 Fmoc-Oic-OH
[Fmoc-L-actahydroindole-2-carboxylic acid]

B-1885 Fmoc-Pen(Acm)-OH

B-1915 Fmoc-D-Pen(Acm)-OH

B-1545 Fmoc-D-Pen(Bzl)-OH

B-2315 Fmoc-Pen-(Trt)-OH

B-2320 Fmoc-D-Pen(Trt)-OH

B-3155 Fmoc-p-phenyl-Phe-OH
[Fmoc- β -(4-biphenyl)-Ala-OH; Fmoc-Bip-OH]

B-3160 Fmoc-p-phenyl-D-Phe-OH
[Fmoc- β -(4-biphenyl)-D-Ala-OH; Fmoc-D-Bip-OH]

B-3195 1-Fmoc-piperidine-4-Fmoc-amino-4-carboxylic acid
[Fmoc-Pip(Fmoc)-OH]

B-3175 Fmoc-4-piperidylacetic acid
[Fmoc-4-carboxymethyl-piperidine]

B-2005 Fmoc- β -(3-pyridyl)-Ala-OH

B-2040 Fmoc- β -(3-pyridyl)-D-Ala-OH

B-3165 Fmoc- β -(2-quinolyl)-Ala-OH

B-3170 Fmoc- β -(2-quinolyl)-D-Ala-OH

B-1665 Fmoc- β -(2-thienyl)-Ala-OH

B-2120 Fmoc- β -(2-thienyl)-D-Ala-OH

B-1920 Fmoc-Tic-OH

B-1925 Fmoc-D-Tic-OH

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B-2470	Fmoc-Tyr(PO ₃ H ₂)-OH
B-1990	Fmoc-Tyr(PO ₃ Me ₂)-OH
B-2275	Fmoc-D-Tyr(PO ₃ Me ₂)-OH
E-2870	Glutaryl-Leu-OH · 2DCHA
G-4490	Hippuryl-Cys(2-aminoethyl)-OH [Bz-Gly-Cys(2-aminoethyl)-OH; BZ-Gly-4-thia-Lys-OH]
F-3815	H- α -Homoethyl-Gly-OH
F-2780	H-Homoarg-OH
F-2995	H-Homocit-OH
F-2735	H-D-Homocit-OH
F-1610	H-Homophe-OH
F-1615	H-D-Homophe-OH
F-1620	H-DL-Homophe-OH
F-1625	H-Homopro-OH
F-1630	H-D-Homopro-OH
F-2915	H-DL-Homopro-OH
F-2465	H-Homopro-OMe · HCl
F-3125	H-D-Homopro-OMe · HCl
F-3330	H-(2S,4S)- γ -Hydroxy-Glu-OH
F-3335	H-(2S,4R)- γ -Hydroxy-Glu-OH
Q-1420	o-Hydroxyhippuric acid [Salicyluric acid]
E-2655	p-Hydroxyhippuric acid
F-1650	H-DL- δ -Hydroxy-DL-Lys-OH · HCl
F-2335	H-DL- δ -Hydroxy-DL-Lys(Boc)-OH
F-3685	H- α -Hydroxy-nor-L-arginine [L-2-Amino-(4-2'-hydroxyguanidino) butyric acid]
F-2935	H-7-Hydroxy-Tic-OH

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F-2990	H-7-Hydroxy-D-Tic-OH
F-1665	H-p-ldo-Phe-OH
F-1670	H-p-ldo-D-Phe-OH
F-1675	H-p-ldo-DL-Phe-OH
F-3350	H-m-ldo-Tyr-OH
F-1695	H-DL-Isoser-OH [H-DL- β -Amino- α -hydroxypropionic acid]
F-1195	Lysinoalanine · 2 HCl (diastereomeric mixture: LL + LD) H-Lys(DL-2-amino-2-carboxyethyl)-OH · 2HCl
F-1765	N-Me-Aib-OH
F-1760	N-Me-allo-lle-Obzl · P-tosylate
F-1795	H- α -Me-DL-His-OH · 2HCl
Q-1585	Melphalan-methyl esler · 2HCl [H-p-Dl(2-chloroethyl)amino-Phe-OMe · 2HCl]
F-1800	H- α -Me-DL-Leu-OH
F-1780	N-Me-p-nitro-Phe-OH
E-3150	H- α -Me-Phe-OH
F-3115	H- α -Me-D-Phe-OH
F-1805	H- α -Me-DL-Phe-OH
F-2805	H- α -Me-DL-Phe-OMe · HCl
F-3780	H-p-Me-Phe-OH
F-3785	H-p-Me-D-Phe-OH
F-3440	H- α -Me-Pro-OH
F-3615	H-2-Mercapto-His-OH
F-3620	H-2-Mercapto-His-OMe
M-2345	H- β -(7-Methoxycoumarin-4yl)-Ala-OH [L-2-Amino-3-(7-methoxycoumarin-4-yl)-propionic acid]
F-3810	1-Methylaminocyclopropone-1-carboxylic acid

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F-1815	H- γ -Methylene-DL-Glu-OH
Q-1645	(2-Methyl-1-indolyl)acetic · DCHA
F-3180	S-Methyl-L-thiocitrulline · acetate
F-2945	H-Met(O)-OH
F-2895	H-Met(O ₂)-OH
F-1810	H- α -Me-DL-Trp-OH
F-2240	H- α -Me-DL-Trp-OMe
F-1820	H-1-Me-DL-Trp-OH
F-3535	H- α -Me-Val-OH
F-3540	H- α -Me-D-Val-OH
F-3355	H- α -Me-DL-Val-OH
F-2550	Myristoyl-Gly-OH
F-1840	H-1-Nal-OH
F-1845	H-D-1-Nal-OH
F-1850	H-DL-1-Nal-OH
F-1855	H-2-Nal-OH
F-1860	H-D-2-Nal-OH
F-1865	H-DL-2-Nal-OH
F-3710	H-2-Nal-Obzl · salt
F-1315	H-Neopentylgly-OH
F-1320	H-D-Neopentylgly-OH
F-1325	H-DL-Neopentylgly-OH
F-3340	H-m-Nitro-p-hydroxy-Phe-OH [H-m-Nitro-Tyr-OH]
F-1895	H-p-Nitro-Phe-OH
F-1900	H-p-Nitro-D-Phe-OH
F-1905	H-p-Nitro-DL-Phe-OH

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F-1910	H-p-Nitro-Phe-OMe · HCl
F-3340	H-m-Nitro-Tyr-OH [H-m-Nitro-p-hydroxy-Phe-OH]
F-3105	H-Oic-OH [L-Octahydroindole-2-carboxylic acid]
F-2515	H-Pan-OH
F-3065	H-Pan(Trt)-OH
F-3645	H-β-Phenyl-Phe-OH [H-β-(4-Biphenyl)-Ala-OH; H-Bip-OH]
F-3650	H-p-Phenyl-D-Phe-OH [H-β-(4-Biphenyl)-D-Ala-OH; H-D-Bip-OH]
F-2040	H-Propargyl-Gly-OH
F-2900	H-D-Propargyl-Gly-OH
F-2860	H-DL-Propargyl-Gly-OH
F-2075	H-Propargyl-Gly-OMe · HCl
F-2825	H-β-(2-Pyridyl)-Ala-OH
F-2790	H-β-(2-Pyridyl)-D-Ala-OH
F-2825	H-β-(2-Pyridyl)-DL-Ala-OH
F-3195	H-β-(3-Pyridyl)-Ala-OH
F-2640	H-β-(3-Pyridyl)-D-Ala-OH
F-3705	H-β-(3-Pyridyl)-DL-Ala-OH
F-3655	H-β-(2-Quinolyl)-Ala-OH
F-3660	H-β-(2-Quinolyl)-D-Ala-OH
F-2030	H-Ser(PO ₃ H ₂)-OH
F-2035	H-D-Ser(PO ₃ H ₂)-OH
F-3365	H-Ser(SO ₃ H)-OH
F-3370	H-D-Ser(SO ₃ H)-OH

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F-1220	Statine [(3S,4S)-4-Amino-3-hydroxy-6-methylheptanoic acid]
F-3665	L-4,5,6,7-Tetrahydرا-1H-imidazo(4,5-c)pyridine-6-carboxylic acid
Q-1535	L-Thiozolidin-2-one-4-carboxylic acid [L-2-Oxothiozolidine-4-carboxylic acid]
F-2955	H-β-(2-Thiazolyl)-DL-Ala-OH
F-2110	H-β-(2-Thienyl)-Ala-OH
F-2115	H-β-(2-Thienyl)-D-Ala-OH
N-1150	H-β-(2-Thienyl)-DL-Ala-OH
F-2120	H-β-(2-Thienyl)-DL-Ser-OH
N-1195	DL-Thiophan [(DL-3-Mercapto-2-benzylpropanoyl)-Gly-OH]
F-2460	L-Thyronine [H-p-(p-Hydroxypheenoxy)-Phe-OH]
F-2405	DL-Thyronine [H-p-(p-Hydroxypheenoxy)-DL-Phe-OH]
F-2580	H-Tic-OH
F-2585	H-D-Tic-OH
F-3310	H-D-Tic-OtBu · HCl
Q-1700	H-Tpi-OH [L-1,2,3,4-Tetrahydronorharman-3-carboxylic acid]
F-3225	H-β-(1,2,4-Triozol-1yl)-DL-Ala-OH
F-3670	H-β-(Ureido)-Ala-OH [H-β-((Aminocarbonyl)amino)-Ala-OH; L-Albizzine]
C-1260	Z-Abu-OH
C-3160	Z-γ-Abu-OH
C-1265	Z-Abu-OSu
C-3350	Z-3-Abz-OSu
C-3680	Z-Aib-OH

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C-3390	Z-allo-Thr(tBu)-OH · DCHA
C-3385	Z-L- α -amino adipic acid [Z-L-2-amino hexanedioic acid]
C-3790	Z-L-2-amino adipic acid- δ -t-butyl ester · DCHA [Z-L-2-amino hexanedioic acid]- δ -t-butyl ester · DCHA]
C-1270	Z- ϵ -aminocaproic acid
C-3975	Z-p-carboxy-Phe(OtBu)-OH
C-3920	Z- β -cyclohexyl-D-Ala-OH · DCHA
C-3705	Z-Dob-OH
C-3770	Z-D-Dob-OH
C-3510	Z-Dob(Boc)-OH · DCHA
C-3765	Z-D-Dob-(Boc)-OH · DCHA
C-3690	Z-Dob(Z)-OH
C-3315	Z-Dop-OH
C-3755	Z-D-Dop-OH
C-3685	Z-Dop(Boc)-OH · DCHA
C-3760	Z-D-Dop(Boc)-OH
C-3695	Z-Dop(Z)-OH
C-1535	Z-dehydro-Ala-OH
C-1540	Z-dehydro-Ala-OMe
C-3525	Z-p-fluoro-Phe-OH
C-3965	Z—D-Homocit-OH [Z- α -amino- ϵ -uneidocaproic acid]
C-1275	Z-Homophe-OH
C-1280	Z-D-Homophe-OH
C-3010	Z-1-Nal-OH
C3950	Z-D-1-Nal-OH
C-3500	Z-2-Nal-OH

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C-2255	Z-D-2-Nal-OH
C-2260	Z-Neopentylgly-OH • DCHA
C-2265	Z-D-Neopenlylgly-OH
C-4030	Z-p-phenyl—Phe-OH [Z- β -(4-biphenyl)-Ala-OH; Z-Bip-OH]
C-4035	Z-p-phenyl-D-Phe-OH [Z- β -(4-biphenyl)-D-Ala-OH; Z-D-Bip-OH]
C-3870	Z-D-Tic-OH

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(54) Title: POLYPEPTIDES, COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS, AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

(57) Abstract: The present invention provides polypeptides, and pharmaceutically acceptable salt thereof, that inhibit the binding of IL-6 ligand with IL-6 receptor under physiological conditions, a nucleic acid that encodes such a polypeptide, an antibody that is specific to such a polypeptide, a composition comprising such a polypeptide, a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, and a method of removing IL-6 ligand from a bodily fluid of an animal.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 86 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 86

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

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